TO STUDY THE OUTCOME OF MEDICALLY (METHOTREXATE) MANAGED CASES OF UNRUPTURED ECTOPIC TUBAL PREGNANCIES

Dissertation submitted
in partial fulfillment of requirements for

M.S. DEGREE BRANCH II

OBSTETRICS AND GYNAECOLOGY
MADRAS MEDICAL COLLEGE
CHENNAI

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI

APRIL 2013

CERTIFICATE

This is to certify that the dissertation entitled **"TO STUDY THE OUTCOME OF MEDICALLY (METHOREXATE) MANAGED CASES OF UNRUPTURED ECTOPIC TUBAL PREGNANCIES"** is a bonafide work done by **DR.P. KAVITHA** in the Institute of Obstetrics and Gynaecology (Madras Medical College) Egmore, Chennai in partial fulfillment of the university rules and regulations for award of MS degree in Obstetrics and Gynaecology under my guidance and supervision during the academic year 2011-2013.

Prof.DR.V.KANAGASABAI M.D
Dean,
Madras Medical College &
Rajiv Gandhi Govt. General Hospital
Chennai – 3

Prof. DR. P.MEENALOCHANI M.D. DGO
Director and Superintendent,
Institute of Obstetrics & Gynaecology
Madras Medical College,
Chennai – 3

Prof. DR.D.TAMILSELVI M.D., DGO
Guide,
Institute of Obstetrics and Gynaecology
Madras Medical College,
Chennai – 3

DECLARATION

I hereby declare that the study titled **"STUDY OF OUTCOME OF MEDICALLY (METHOTREXATE) MANAGED CASES OF UNRUPTURED ECTOPIC TUBAL PREGNANCY"** was done by me in the Institute of Obstetrics and Gynaecology (IOG), Madras Medical College, Chennai – 600 003, during the period of my PG study for M.S Obstetrics and Gynaecology from 2011-2013, under the guidance and supervision of, **Prof.Dr.D.TAMILSELVI M.D., DGO.**

This dissertation is submitted to the TamilNadu **Dr. M.G.R. Medical University**, Chennai in partial fulfillment of University regulations for the award of M.S. Degree Examination in Obstetrics and Gynaecology.

Signature of Candidate
DR. P. KAVITHA
M.S., P.G (Obsetrics and Gynaecology)
Institute of Obsetrics and Gynaecology
Madras Medical College,
Chennai -3.

Place : Chennai-3
Date:

Prof. DR.D.TAMILSELVI,M.D., DGO
Guide,
Institute of Obstetrics and Gynaecology,
Madras Medical College,
Chennai – 3.

ACKNOWLEDGEMENT

I gratefully acknowledge and sincerely thank **Prof.Dr.V.KANAGASABAI, M.D,** DEAN**,** Madras Medical College and Rajiv Gandhi Govt.General Hospital, Chennai 600003 for permitting me to conduct the study and use the facilities of the Institution for my study.

I am grateful to the Director and Superintendent, **Prof.Dr.P.MEENALOCHANI, M.D.,DGO,** Institute of Obstetrics & Gynaecology, Egmore,Chennai, for her guidance.

I am extremely thankful to our Deputy Superintendent, **Prof. Dr. RUKKMANI, M.D., D.G.O.,** for her support in conducting this study.

Dr. JAYA, M.D., D.G.O., Former Director and Superintendent, Institute of Obstetrics and Gynaecology, Egmore for granting me permission to utilize the facilities of the institute for my study.

I wish to express my deep sense of gratitude to **Prof.Dr.D.TAMILSELVI, M.D., D.G.O.,** for her valuable guidance and supervision throughout my study.

I am thankful to the RMO and all UNIT CHIEFS for their support, advice and encouragement.

My special thanks to **Dr. MOHANRAM DMRT** and **Dr.VIJAYALAKSHMI. M.D (RT),** of the Radiology Department for their co-operation and help for conducting this study.

I am thankful to all Assistant Professors and Teachers for their guidance and help.

I thank my husband and my family members for their constant encouragement and moral support throughout this study.

Last, but not the least, I thank all my patients for their kind co-operation who made this study feasible.

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To

PG in MS Obstetrics & Gynaecology
Instt. of Obstetrics & Gynaecology
Egmore, Chennai -8

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "A Prospective study on the outcome of medical (methotrexate) managed cases of unruptured ectopic tubal pregnancies" No.15082012.

The following members of Ethics Committee were present in the meeting held on 10/08/2012 conducted at Madras Medical College, Chennai -3.

1. Dr. S.K. Rajan. M.D.,FRCP.,DSc	-- Chairperson
2. Prof. Pregna B. Dolia MD Vice Principal, Madras Medical College, Chennai -3 Director , Institute of Biochemistry, MMC, Ch-3	-- Member Secretary
3. Prof. B. Vasanthi MD Prof of Pharmacology ,MMC, Ch-3	-- Member
4. Prof. C. Rajendiran, MD Director , Inst. Of Internal Medicine, MMC, Ch-3	-- Member
5. Prof. S. Deivanayagam MS Prof of Surgery, MMC, Ch-3	-- Member
6. Thiru. S. Govindsamy. BABL	-- Lawyer
7. Tmt. Arnold Soulina MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

CONTENTS

INTRODUCTION

In 1876, Sir John S. Parry Wrote:

"….when one is called to a case of this kind, it is his duty to look upon his unhappy patient as inevitably doomed to die, unless he can by some active measure wrest her from the grave already yawning before her."

The first recorded case of ectopic pregnancy is that of Albucasis in the 11th Century. The modern management of ectopic pregnancy is one of medicine's greatest success stories.

The term Ectopic is derived from the Greek word "Ek and to-pos", meaning "out of place or displaced". Ectopic pregnancy is defined as the implantation of fertilized ovum or blastocyst anywhere other than in a normal uterine cavity. This includes tubal pregnancies and non-tubal pregnancies involving the ovary, cornual region of the uterus, rudimentary uterine horn, the abdominal cavity, and in the cervix. This abnormally implanted gestation grows and draws its blood supply from

the site of abnormal implantation. As the gestation enlarges, it creates the potential for organ rupture because only the uterine cavity is designed to expand and accommodate fetal development. Ectopic pregnancy can lead to massive hemorrhage, infertility, or death.

MILESTONES IN EVOLUTION OF ECTOPIC PREGNANCY AND ITS MANAGEMENT:

1535 – Begnegario – De – Capri described a case of secondary abdominal pregnancy.

1595 – Only recorded attempts of surgery by Jacob Noirus and Felic Plater-1598.

1681 – Rionis first described a pregnancy in rudimentary horn of uterus.

1873 – Barnes introduced the term ectopic gestation.

1882 – Spiegelberg introduced criteria to diagnose ovarian pregnancy.

1883 – Robert Lawson Tait of Birmingham in London, pioneered a new concept, timely surgical intervention could be life saving.

1894 – Bussuere presented a case of unruptured ectopic gestation.

1896 - Galabain presented a case of primary abdominal pregnancy.

1911 – Rubin published criteria to diagnose cervical pregnancy.

1972 – Stepter and Edwards reported a case of tubal pregnancy following In Vitro Fertilization.

1982- Treatment of an interstitial ectopic pregnancy in a patient with a 15day course of intramuscular methotrexates was reported by Tanaka et al.

1991 – Stovall et al (University of Tennessee, Memphis, TN) concluded that methotrexate/ citrovorum treatment is safe and helps to preserve the reproductive potential.

There is a decrease in the maternal mortality rate due to great improvement in anesthesia, blood transfusion and antibiotics. In the early half of the 20^{th} Century, 200-400 deaths per 10,000 cases were attributed to ectopic pregnancy. In 1970, the Centre's for Disease Control and Prevention (CDC) began to record the statistics regarding ectopic pregnancy, reporting 17,800 cases. By 1992, the number of ectopic pregnancies had increased to 108,800. Concurrently, however, the case-fatality rate decreased from 35.5 deaths per 10,000 cases in 1970 to 2.6 per 10,000 cases in 1992. With earlier diagnosis both maternal survival and conservation of reproductive capacity are enhanced.

AIM OF STUDY

- To study the outcome of medically managed cases of unruptured tubal ectopic pregnancies using intramuscular methotrexate.
- To study the association of outcome with the following parameters:
  1. Initial β – hCG levels
  2. Adnexal mass size
  3. Period of amenorrhea
  4. Presence or absence of cardiac activity

REVIEW OF LITERATURE

Ectopic pregnancy is defined as implantation of fertilized ovum in a site other than the uterine cavity.

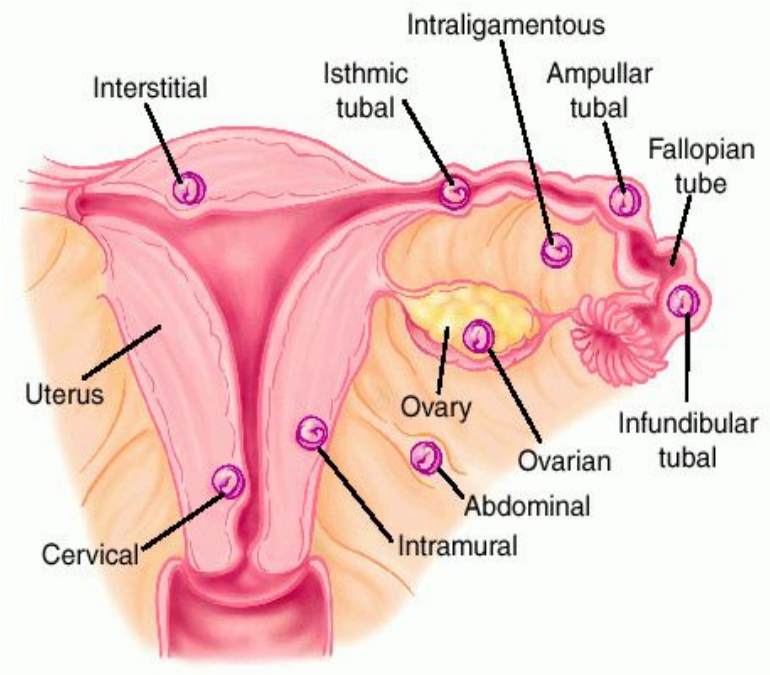


Figure 1: Types of Ectopic Pregnancies

SITES OF IMPLANTATION

TUBAL

About 95 percent of ectopic pregnancies are situated in the fallopian tube: 54% - ampulla; 24%- isthmus; 16% -frimbria ; 1.9 percent in the interstitial region. When the ovum embedded in ampulla, several modes of termination are possible:

1. Tubal mole
2. Tubal abortion
3. Tubal rupture or perforation
4. Continuation of pregnancy till later months or even to term

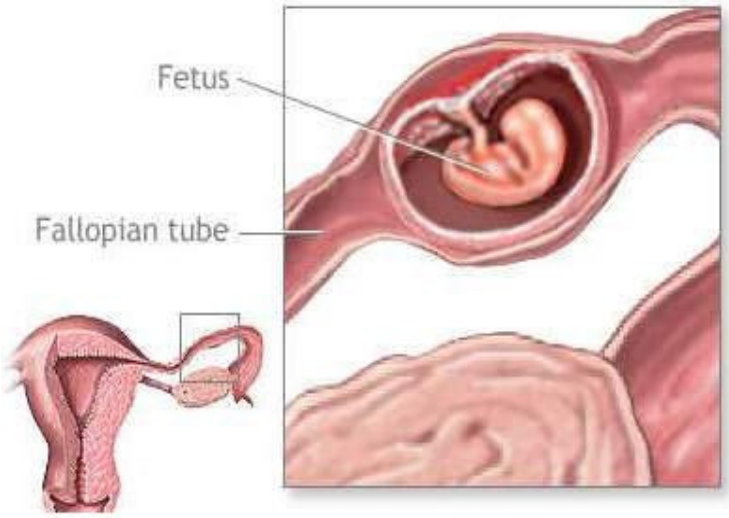


Figure 2: Blastocyst implanted in the fallopian tube

NON TUBAL

- OVARIAN
- CERVICAL
- ABDOMINAL
- HETEROTOPIC
- INTERSTITIAL
- INTERLIGAMENTOUS
- CAESAREAN

OVARIAN PREGNANCY :

Ectopic pregnancies implanted in the ovary is rare.

Causes: Traditional risk factors for Tubal pregnancy are similar for ovarian pregnancy. Concurrent use of an intrauterine contraceptive device (IUD) seems to be inordinately associated with ovarian pregnancy. **Spiegelberg's (1878) Criteria for Pathological Diagnosis of Ovarian Pregnancy**

- The ipsilateral tube is intact and distinct from the ovary.
- The ectopic pregnancy occupies the ovary.

- The ectopic pregnancy is connected by the uteroovarian ligament to the uterus.
- Ovarian tissue can be demonstrated histologically in the placental tissue.

Treatment :

1. Ovarian cystectomy, Laparoscopic laser surgery,
2. Methotrexate for unruptured ovarian pregnancy,
3. Uncontrollable hemorrhage necessitates oophorectomy or salpingo – oophorectomy.

CERVICAL PREGNANCY:

It is defined as the implantation of gestational tissue within the endocervical canal.

***Incidence*:** 1:8,600 to 1: 12,400 pregnancies.

Cervix is rare but hazardous site for placental implantation because the trophoblast can penetrate through the cervical wall and into the uterine blood supply, resulting in profuse bleeding.

Causes : Previous induced abortion, Ashermann's procedure, Previous caesarean delivery, DES exposure, Leiomyomata, In vitro fertialization and embryo transfer.

Rubin's (1911) criteria for diagnosis of cervical pregnancy:

- Cervical glands must be present opposite the placental attachment site.
- A portion of or the entire placenta is located below either the entrance of the uterine vessels or below peritoneal reflection on the anteroposterior uterine surfaces.
- Fetal elements must not be present in the uterine corpus.

The Clinical Criteria for diagnosis of Cervical Pregnancy, as Defined by Paalman and Mcelin, include

1. Amenorrhoea followed by painless uterine bleeding,
2. Softened and disproportionately enlarged cervix(hour – glass – shaped uterus)
3. Products of conception entirely confined within and firmly attached to endocervical canal
4. A snug internal os and
5. A partially open external os.

Treatment :

1. Evacuation of pregnancy by suction curettage after vascular ligation or lateral cervical suture placement to ligate lateral cervical vessels.
2. Controlling hemorrhage with uterine packing, insertion of intracervical 30ml foley's catheter to tamponade bleeding, angiographic arterial embolization.
3. Treatment with systemic and local MTX either alone or in combination with cervical instrumentation (Timor – Tritsh et al 1994).
4. TVS guided injection of Kcl into gestational sac (Frates, 1994).
5. Oral etoposide (Segma, 1990) or intravenous actinomycin – D (Brand et al, 1993).

ABDOMINAL PREGNANCY

Classified as 1.Primary abdominal pregnancy

2. Secondary abdominal pregnancy

STUDDIFORD'S criteria for primary abdominal pregnancy:

1. Presence of normal tubes and ovaries with no evidence of recent or past pregnancy.
2. No evidence of uteroperitoneal fistula.
3. The presence of a pregnancy related exclusively to the peritoneal surface and early enough to eliminate the possibility of secondary implantation after primary tubal nidation.

DIAGNOSIS:

Physical examination, persistent abnormal fetal lie, abdominal tenderness, a displaced cervix, easy palpation of fetal parts, palpation of a uterus separate from the gestation, no uterine contractions after oxytocin infusion. Abdominal X-ray, Abdominal ultrasonogram, CT, MRI can be used to diagnose abdominal pregnancy.

Treatment :

Because the pregnancy can continue to term, maternal morbidity and mortality is very high, recommending surgical intervention. Perinatal mortality results from growth restriction and congenital anamolies (20-40%).

HETEROTOPIC PREGNANCY:

Heterotopic pregnancies were rare, with an incidenc of 1 in 30,000. Currently because of assisted reproduction, incidence is likely to be 1 in 7000 overall, and following ovulation induction it may be as high as 1 in 900(Gaussner & associates 1990). The risk is as high as 2-3% among patients undergoing assisted reproduction. Causes of heterotopic pregnancy include ovulation induction, IVF-ET, Pelvic Inflammatory Disease.

Surgery is the treatment of choice. MTX is contraindicated due to detrimental effects on the normal pregnancy.

INTERSTITIAL PREGNANCY:

Incidence **:** Accounts for 2-4% of all tubal gestations.

Because of the proximity to the uterine and ovarian arteries, there is a risk of severe haemorrhage.

Treatment: Choice of treatment depends on the extent of trauma in the uterine wall and child bearing function of the patient.

1. Cornual resection & repair of the defect either by laparotomy or laparoscopy.
2. Medical treatment with local or systemic MTX.
3. Local instillation of Kcl into ectopic gestational sac.
4. Hysteroscopic resection of interstitial pregnancy.
5. Hysterectomy.

INTERLIGAMENTOUS PREGNANCY

***Incidence*:** 1 in 300 ectopic gestations

Interligamentous pregnancy results from trophoblastic penetration of a tubal pregnancy through the tubal serosa and into the mesosalpinx, with secondary implantation between the leaves of the broad ligament.It also occurs if a uterine fistula develops between the endometrial cavity and the retroperitoneal space.

The timing, extent and complications of surgery are similar to those of an abdominal pregnancy except that as the pregnancy is wholly extraperitoneal,torrential haemorrhage is less likely.

PERSISTANT ECTOPIC PREGNANCY

***Incidence*:** 3-20%

Persistent ectopic pregnancy occurs when a patient has undergone conservative surgery and viable trophoblastic tissue remains.

Diagnosis

1. Lack of fall, or plateuing of hCG level after conservative surgery.
2. Initial measurement of serum hCG or progesterone 6 days post operatively and 3-day interval thereafter does not show any fall on the other hand may even increase.

Risk factors

1. Type of surgical procedure
2. Initial HCG levels
3. Duration of amenorrhea
4. Size of ectopic pregnancy

Treatment:

1. Medical therapy with methotrexate given as a single intramuscular injection in the dose of 50 mg/sq.m body surface area.
2. Surgical therapy consist of either repeat salpingostomy or salpingectomy.

ETIOLOGY AND RISK FACTORS

Ectopic pregnancy most often is associated with risk factors leading to tubal damage and altered embryo transport.

Table 1: Etiologies of Ectopic Pregnancy

ANATOMIC	HORMONAL	EMBRYONIC
Infection	Premature ovulation	Altered implantation
Inflammation	Delayed ovulation	Blighted embryo
IUD	Hyperestrogenism	
Previous surgery	Pergonal/clomid	
Prior induced abortion	In Vitro fertilization	
Diethylstilbesterol		
Recurrent miscarriage		

Table 2: Risk Factors for Ectopic Pregnancy

RISK FACTORS	ODDS RATIO
Previous ectopic pregnancy	12.5
Tubal corrective surgery	4
Tubal Sterilization	9
Intra uterine device	1-4.2
Document tubal pathology	3.8-21
Infertility >1year	2.5-3
Assisted reproductive technology	2-8
Previous genital infections	3.4
Multiple sexual partners	1.6-3.5
Prior abortion	0.6-3
Cigarette Smoking	1.7-4
Prior cesarean delivery	1-2.1
Age>40 years	2.9

PATHOGENESIS:

First, the conceptus and corpus luteum may be completely normal, but the fallopian tube is somehow blocked or damaged. In such cases the trophoblast proliferates normally and quickly invades the sub epithelial spaces. Secretion of β -hCG and progesterone initially is similar to that of normal pregnancy and patient has no symptoms. As the trophoblast

begins to erode into small submucosal arterioles, hematoma formation occurs. This distends the tubal serosa and produces pelvic pain and an easily visualized bluish swelling within the tube. At this point the production of beta-hCG and progesterone usually begins to falter, there is insufficient support for the early corpus luteum, and patient starts having abnormal uterine bleeding.

Second, the tube and corpus luteum may be normal, but the conceptus is abnormal (blighted ovum), creating a predispostition to ectopic nidation. In this case, initially serum beta-hCG and progesterone levels would be abnormally low early in course of gestation like a blighted ovum in Intra Uterine Pregnancy.

Third, the conceptus and tube may be normal, but corpus luteum function is not. In this case initially normal beta-h CG levels can be expected, but progesterone will be abnormally low.

DIAGNOSIS

1. Patient history
2. Physical examination
3. Endocrine markers
4. Ultrasonography
5. Doppler Ultrasound
6. Culdocentesis
7. Laparotomy
8. Laparoscopy
9. Histopathology

Patient History and Physical Examination

Table 3: Symptoms of Ectopic Gestation

Symptoms	% of Ectopics with Symptom
Abdominal pain	95-100
Amenorrhea	75-95
Abnormal uterine bleeding	65-85
Dizziness	20-35
Urge to defecate	5-15
Pregnancy symptoms	10-25
Nausea	15

Table 4: SIGNS OF ECTOPIC PREGNANCY

Signs	Patients with sign %
Adnexal tenderness	75-90
Abdominal tenderness	80-95
Adnexal mass	50
Uterine enlargement	20-30
Orthostatic changes	10-15
Fever	5-10

Multimodality Diagnosis

1) **Serial Beta- hCG Assays:** Human chorionic gonadotropin is a glycoprotein produced by syncytiotrophoblast. The serum beta – hCG radioimmunoassay is the gold standard for evaluating trophoblast activity. In ectopic pregnancy, the serum beta-hCG tends to be lower than with a viable IUP given the same gestational age. For patients with tubal pregnancies, higher serum beta-hCG levels correlate with the tubes being ruptured, the size of eccyecis, and volume of hemoperitoneum. It is detected in the serum 8 days after the luteinizing hormone (LH) surge and in the urine 13 days after

ovulation around the time of implantation. Most qualitative blood pregnancy tests are considered positive with an HCG level of 30mlU/ml, 14 days post conception. With a robust uterine pregnancy, serum b-hCG should increase atleast 66% every 48hours. Beta-hCG doubles every two days in a normal IUP. A 66% rise in the beta-hCG level over 48 hrs (85% confidence level) represents the lower limit of normal values for viable intrauterine pregnancy. 15% of healthy intrauterine pregnancies do not increase by 65% and that 13% of all ectopic gestations have normally rising beta – hCG of atleast 65% in 48 hours.The beta-hCG pattern that is most predictive of ectopic pregnancy is one that has reached a plateau (a doubling time of more than 7 days). For falling levels, a half life a less that 1.4 days is rarely associated with ectopic pregnancy, where as a half life more than 7 days is most predictive of ectopic pregnancy.

2) **CA-125**: CA-125 has been increased in women with epithelial ovarian cancer, acute pelvic inflammatory disease, and early normal pregnancy. In a prospective single blind and controlled study done by Erdal et al found that in intact tubal pregnancies, the increase of CA-

125 levels in the serial measurements could be a supplementary test for an early diagnosis of tubal rupture in patients with expectant or medical management.

3) **PAPP-**A: The Pregnancy associated plasma protein – A Sjoberg measured serum PAPP-A concentrations in 164 patients presented to gynaecologic emergency services: 124 women had EP and 40 had intrauterine abortions. The PAPP-A levels in 136 women with normal IUP were compared with those of 460 non-pregnant women. Serum PAPP-A levels were lower in the EP and intrauterine abortion groups compared to the normal pregnancy group; they were undetectable in 82% of the EP group and 55% of the intrauterine abortion group.

4) **Serum Progesterone:** is used by Stovall(1992) to diagnosis ectopic pregnancy when serum b-hCG and sonographic findings are inconclusive.There is minimal variation in serum progesterone levels between 5 and 10 weeks gestation, thus a single value is sufficient. Mol (1998) performed a meta-analysis of 22 studies to assess the accuracy of single serum progesterone measurement to differentiate

ectopic from uterine pregnancy. The meta-analysis revealed that low levels of serum progesterone (<5ng/ml) could be used to correctly diagnose pregnancy failure, but cannot differentiate between an ectopic and uterine pregnancy.

5) **Pregnanediol-3 Alpha-Glucuronide:** Sauer and coworkers reported that a rapid enzyme immunoassay for levels for urinary pregnannediol-3 alpha-glucuronide correlated well with serum progesterone levels and were also consistently below expected levels in 60 patients with ectopic pregnancies.

6) **Relaxin**

7) **Maternal Serum Alpha Fetoprotien and Cell Free Fetal DNA**

8) **C – Reactive Protein**

9) **VGEF:** VGEF is a potent angiogenic factor that acts as a modulator of vascular growth, remodeling, and permeability in the endometrium, decidua, and trophoblast, as well as during vascular development in

the embryo, all of which are crucial process related to normal implantation and placentation. Felemban et al concluded that VEGF concentrations are higer in women with EP than in those with normal and arrested IUP. Daponte et al described higher serum VEGF concentrations in women with EP (median pg/ml) than in those with abnormal intrauterine pregnancy (median 107.2pg/ml) ($P<0.001$).

10) **Serum Creatine Kinase:** The lack of a sub mucosal layer in the fallopian tube allows zygote to penetrate the epithelium and lay next to the muscular layer in tubal pregnancies. The trophoblast usually invades the muscle layer and maternal blood vessels are eroded, allowing muscle cell products such as CK to enter the circulation; therefore, increased serum CK levels are normal during EP. Katsikis et al studied 40 women with EP 20 with intrauterine abortive gestation and 20 normal pregnant women (controls). Total serum CK levels were measured at the time of presentation and 24 hours after surgery. Women with EP had significantly higher CK concentrations compared to women with intrauterine abortive pregnancies and controls.

11) **Pregnancy Specific B1 Glycoprotein (Shwangerschaft Protein):**

12) **Renin:**

13) **Inhibin-**A:

Sonography

High resolution sonography has revolutionized the clinical management of women with ectopic pregnancy. The imaging modality of choice for the diagnosis of ectopic pregnancy is Transvaginal sonography(TVS) with overall reported sensitivities of >90%. In the large study of more than 1200 patients by Barnhart et al, 78.8% of patients were diagnosed definitely at the initial visit using an algorithm that included the use of USG along with serum beta-hCG levels above the discriminatory zone.

According to this study, if the patient's serum beta-hCG level was above the established discriminatory zone at initial presentation and an intrauterine sac was not identified, an operative approach involving

curettage and possible operative laparoscopy was used to diagnose ectopic pregnancy. Combined transvaginal ultrasonograpy and serial quantitative beta-hCG measurements are approximately 96% sensitive and 97% specific for diagnosing ectopic pregnancy. Therefore, transvaginal ultrosonography followed by quantitative beta-hCG testing is the optimal and most cost-effective strategy for diagnosing ectopic pregnancy. It is reported that using TAS, an intra-uterine sac can be visualized when the serum beta-hCG is >6500 IU/L. However with a TVS an intrauterine sac should be visualized with serum beta-hCG as low as 1000 IU/L. The use of TVS in the diagnosis of ectopic pregnancy has become widely accepted and practiced. Transvaginal ultrasonography has transformed the assessment of problems in early pregnancy. In fact,Condous, upholds that “transabdominal ultrasonography is outdated modality which is not diagnostic of ectopic pregnancy and should no longer be used”. Majority of studies show TVS to be an accurate diagnostic test for ectopic pregnancy with a high sensitivity of 87-99% and specificity of 94-99%. Shalev and colleagues found that the use of TVS in the diagnosis of an ectopic pregnancy has a sensitivity of 87%, specificity of 94%, and positive predictive value of 92.5%. Another study

gave a sensitivity of 93%, specificity of 99%, and positive predictive value of 98%, and when a TVS finding of an adnexal mass was combined with serum beta-hCG, this increased the sensitivity of 97%, with equivalent specificity and positive predictive value.

To make the diagnosis, an ectopic mass should be seen in adnexa separate to the ovary and an empty endometrial cavity. The following may be visualized:

1. An inhomogeneous adnexal mass.
2. An empty extra – uterine sac with a hyper-echoic ring or bagel ring.
3. A yolksac and /or a fetalpole with or without cardiac activity in the extra-uterine sac.

Sometimes there are no conclusive adnexal findings, and the diagnosis of ectopic pregnancy may be based on the other ultrasound features, such as hemoperitoneum, hematosalpinx, and free fluid in the peritoneum or the pelvis, for example, in the pouch of Douglas.

Discriminatory Zone:

In the management of suspected ectopic pregnancy there is a serum hCG level at which it is assumed that all viable intrauterine pregnancies will be visualized by transvaginal ultrasound. This is referred to as the discriminatory zone.

When serum hCG levels are below the discriminatory zone (<1000 IU) and there is no pregnancy (intra-or extra uterine) visible on transvaginal ultrasound scan, the pregnancy can be described as being of unknown location. The concept of a discriminatory zone has limitations. Levels of hCG of 1000 IU/L, 1500 IU/L and 2000 IU/L have been used as discriminatory levels.

Table 5: Transvaginal Ultrasound Findings in Ectopic Pregnancy

Finding	LR*
Ectopic cardiac activity	>100(diagnostic)
Ectopic gestational sac	23
Ectopic mass and fluid in pouch of Douglas	9.9
Fluid in pouch of Douglas	4.4
Ectopic mass	3.6
No intrauterine gestational sac	2.2
Normal adenexal region	0.55
Intrauterine gestational sac	0.07

LR = likelihood ratio.

*_An LR > 5 - moderately strong evidence

LR > 10 - strong evidence

LR < 0.1 is strong evidence against ectopic gestation.

DOPPLER ULTRASOUND:

The waveform in the uterine arteries in the nongravid state in the first trimester of pregnancy shows a high resistance (little or no flow), low velocity pattern. Conversely a high velocity, low resistance signal is localized to the area of developing placentation. This pattern seen near the endometrium is associated with normal and abnormal intrauterine pregnancies and is termed peritrophoblastic flow.The combined use of Doppler and two dimensional imaging allows the differentiation of pseudogestational sacs and true intrauterine gestational sacs. It also improves the diagnostic sensitivity for individual diagnosis from 71% to 87% for ectopic pregnancy, from 24% to 59% for failed intrauterine pregnancy and from 90% to 99% for normal intrauterine pregnancy. With transvaginal colour Doppler imaging, placental blood flow within the periphery of the complex adnexal mass-the ring of fire is seen.

CULDOCENTESIS

Historically, culdocentesis was an easy bedside test used to diagnose hemoperitoneum.With the use of hCG testing and transvaginal ultrasound, culdocentesis is rarely indicated.

ENDOMETRIAL SAMPLING

If the patient is bleeding excessively and requires a D & C, the removed products are sent for histopathological examination. Decidua without chorionic villi although suggests but does not confirm the diagnosis of ectopic pregnancy as these findings occur with spontaneous abortions as well.

LAPAROSCOPY

Laparoscopy facilities early diagnosis of ectopic pregnancy. It has reduced the clinical error in diagnosing an ectopic pregnancy to less than 4% of cases and the simpler technique has limited the need for laparotomy.

Indications

1. When unruptured ectopic is suspected but patient has signs of intraperitoneal bleeding.
2. When patient has beta-hCG levels less than 6500 mIU/ml on a negative ultrasound.
3. Patients who have less than 66% increase in beta-hCG over 48 hrs.

MANAGEMENT

1. Expectant management
2. Medical treatment
3. Salpingocentesis
4. Surgical treatment.

EXPECTANT MANAGEMENT

Expectant management is between 88 & 96 percent effective in managing ectopic pregnancy when the initial β-hCG values<200IU/L.

Criteria

1. Falling HCG titre
2. Ectopic pregnancy definitely in the tube
3. No significant bleeding
4. No evidence of rupture
5. Ectopic mass no larger than 3.5cm in greatest diameter

Expectant management included the monitoring of clinical symptoms, HCG titers, and ultrasonographic findings. Approximately one fourth of patients presenting with ectopic pregnancy can be managed expectantly and 70% of this select group will avoid surgery and experience successful outcomes. Success with expectant management decreases with rising HCG levels. Best results are achieved when initial HCG levels are below 200IU/L. An argument could be made that minimal side effects of methotrexate make it preferable to a potentially prolonged surveillance and associated patient anxiety.

MEDICAL TREATMENT

Medical therapy is preferred by most, if feasible**.** In the United States, during 2002-2007, the percentage of patients treated with methotrexate increased from 11% to 35%.Comparison of medical and surgical treatment of small intact extrauterine pregnancies also revealed similar success and subsequent spontaneous pregnancy rates in a prospective randomized trial done by Moeller et al.

Methotrexate

Methotrexate formerly known as amethopterin, is an antimetabolite drug that inhibits dihydrofolate reductase-blocking the conversion of dihydrofolic acid to tetrahydrofolic acid which is an essential coenzyme required for 1 carbon transfer reactions in *de novo* purine synthesis. Methotrexate has cell cycle specific action – kills cells in S phase; primarly inhibits DNA synthesis.

Table 6: Case Series using Expectant Management for Treatment of Ectopic pregnancy

Study	Year	Patients	Success	Tubal Patency	Intrauterine Pregnancy	Recurrent Ectopic Pregnancy
Land	1955	119	68(57)	NR	32/43	11/43
Mashiach et al	1982	5	4(80)	1/1	NR	NR
Carp et al	1986	14	11(79)	5/5	3/5	1/5
Adoni et al	1986	11	11(100)	NR	NR	NR
Dericks Tan et al	1987	12	12(100)	NR	NR	NR
Garcia et al	1987	13	12(92)	7/10	3/3	0/3
Fernandez et al	1988	14	9(64)	NR	NR	NR
Seuer et al	1987 1989	10	10(100)	NR	NR	NR
Makinen et al	1990	35	27(82)	NR	NR	NR
Carson et al	1991	8	5	NR	NR	NR
Korhonen et al	1994	118	77(65)	NR	NR	NR
Shalev et al	1995	60	28(47)49(73)	NR	NR	NR
Brio et al	1995	67	49(73)	NR	NR	NR
Total		198	137(69)	13/16	38/51	12/51

Methotrexate: Pharmacokinetics

Methotrexate is a weak dicarboxylic acid with pKa 4.8 and 5.5, and thus it is mostly ionized at physiologic pH. Oral absorption is saturatable and thus does-dependent, with doses less than 40 mg/m^2 having 42% bioavailability and doses greater than 40 mg/m^2 only 18%. Mean oral bioavailability is 33% (13-76% range), and there is no clear benefit to subdividing an oral dose. Mean intramuscular bioavailability is 76% Methotrexate is metabolized by intestinal bacterial to the inactive metabolic 4-amino-4-deoxy-N-methylpteroic acid (DAMPA) and accounts for less than 5 % loss of the oral dose. Factors that decrease absorption include food, oral non-absorbable antibiotics (e.g. vancomycin, neomycin, and bacitracin), and more rapid transit through the gastrointestinal tract (GI) such as diarrhea, while slower transit time in the GI tract from constipation will increase absorption.

Treatment and side effects associated with MTX: Methotrexate is a highly tertogenic drug and categorized in Pregnancy Category X by the FDA

Treatment effects:

- Increase in ectopic mass by Ultrasound
- Increase in HCG during initial therapy
- Vaginal bleeding or spotting
- Abdominal pain (separation pain)

Drug side effects:

- Nausea, Vomiting
- Stomatitis
- Dizziness
- Gastic distress
- Serve neutropenia(rare)
- Reversible alopecia(rare)
- Pneumonitis (rare)

Table 7: Success Rate -Methotrexate Therapy

at Various Baseline Beta-hCG Level.

Initial beta-hCG level (mIU/mL)	**Success rate (%)**
Less than 1,000(1,000 IU per L)	98
1,000 to 1,999(1,000 to 1,999IU per L)	93
2,000 to 4,999(2,000 to 4,999 IU per L)	92
5,000 to 9,999(5,000 to 9,999 IU per L)	87
10,000 to 14,999(10,000 to 14,999 IU per L)	82
15,000 or greater(15,000 or greater IU per L)	68

Table 8: Case Series using Methotrexate as Primary Treatment for Ectopic Pregnancy

Study	Year	No. of Patients	Success	Dosage	Patency Rate	Laparotomy Needed	Toxicity
Myazaki et al	1983	18	7(88)	30-60 MG I/M	4/5(80)	1	-
Ory et al	1986	7	6(86)	1MG/KG 4days IV	4/7(57)	1	5
Goldstein	1986	7	6(86)	1MG/KG 4days IM	4/4(100)	1	0
		6	6(100)	200MG / M^2	-	0	0
Sauer et al	1987	21	20(95)	1MG/KG 4days IM	15/20(75)	1	5
Ichino et al	1987	23	22(96)	0.4 MG/KG 5days IM	10/19(53)	1	5
Stovall et al	1989	36	34(94)	1MG/KG 1-5 days IM	-	2	3
TOTAL		108	101(94)	-	43/62(70)	7	18

CRITERIA FOR PATIENT SELECTION

1. Patient is healthy, hemodynamically stable, reliable and complaint.
2. Ultrasonography should fail to find an intrauterine pregnancy, and uterine curettage should fail to obtain villi.
3. Ectopic pregnancy should measure less than 4 cm in its greatest diameter
4. HCG titers >10,000 IU/L and presence of fetal heart rate are relative contraindications. However even patient with fetal cardiac activity, success rate of 87% has been reported.

Single Dose Regimen of Methotrexate for Treatment of Ectopic Pregnancy

The average success rates for the single-dosage regimen are reported to be from 88-94%. In a study by Stoval and Ling, 113 patients (94%) were treated successfully, 4 (3.3%) of whom needed a second dose.

- DAY 1 : Baseline Studies,
  β-hCG
  Methotrexate 1mg/kg i.m
- DAY 4 : β -hCG Titer
- DAY 7 : β -hCG Titer
- Weekly : β -hCG Titer becomes Negative

In a prospective review of 110 patients, conducted by Thia et al from Aug 2003 to Oct 2006, 87(79.1%) patients were treated successfully with single dose of MTX following the above regimen. 6(5.4%) required second dose and 16(14.5%) patients underwent surgery and only one patient defaulted on followup. In this cohort study, there was no major side effect detected. Mucositis (19%) and abdominal pain (28 %) were minor side effects.

In a prospective interventional study done on 11 patients by Merisio et al from Dec 2002 to Apr 2003, single dose MTX were treated for 10(90%) whereas 1(10%) patient required second dose. None of the patients had to undergo laparotomy.

In a retrospective cohort study done by Mamdoh et al, Ectopic pregnancy was diagnosed for 70 women and were treated with single dose MTX (50mg/kg).After a single dose, 66(94%) patients experienced ectopic resolution, 3(4%) patients needed a second dose of MTX, and 1(1.5%) patient has a subsequent tubal rupture.

By the 3rd day, there is increase in the beta-hCG levels and is not significant. A decrease in the beta-hCG levels of at least 15% from days four to seven post injection shows a successful medical treatment. A systemic review conducted by Menon et al, supports that when the initial beta-hCG is above 5,000 mIU/mL, there is an increase in failure of medical treatment with single-dose methotrexate. So, above this β-hCG level, Methotrexate should be used with caution.

A hybrid protocol, involving 2 equal doses of methotrexate (50 mg /m^2) given on days I and 4 without the use of leucovorin has been shown to be an effective and convenient alternative to the existing regimens. Success rates were 81.5% for expectant management, 90% for medical management, and 91% for surgical management.

Methotrexate -Multiple Dose Regimen

- DAY 1 : Methotrexate 1.0mg/kg i.m

  Hb, TC/DC, Platelet count, RFT/LFT,

  Serum beta-hCG.
- DAY 2 : Folinic Acid 0.1 mg/kg i.m.
- DAY 3 : Methotrexate 1.0mg/kg i.m

  Beta-hCG Titer
- DAY 4 : Leucovorin 0.1 mg/kg i.m
- DAY 5 : Methotrexate 1.0mg/kg i.m.

  Beta-hCG Titer
- DAY 6 : Leucovorin 0.1 mg/kg i.m
- DAY 7 : Methotrexate 1.0mg/kg i.m.

  Beta-hCG Titer
- DAY 8 : Folinic Acid 0.1 mg/kg i.m

  Complete blood and platelet counts, liver and renal function tests
- WEEKLY : Beta-hCG Titer Till Negative or <5 mIU/ml

- Treatment is declined when a decline of >15% is observed in two consecutive daily counts, or after 4 doses of methotrexate.
- Weekly titers are done and second course of treatment is requirement if beta-hCG titers plateau or rise.

In a 2003 meta-analysis , single-dose regimen were given for 20 patients, and multiple-dose regimen for 6 patients.There was fewer side effects with single dose regimen but was less effective. The success rate was 88% compared with the multiple-dose regimen's 93% success rate. The overall success rate was 89% regardless of the protocol.

A prospective randomized trial conducted by Guvendag et al showed that multiple dose methotrexate regimen for the treatment of unruptured tubal ectopic pregnancy is not more effective than a single dose one. In addition, multiple doses may cause more side-effects, but the time for beta-hCG levels to fall below 5 mUI/mL is shorter.

SALPINGOCENTESIS

It is a technique in which methotrexate, prostaglandin f2 alpha, potassium chloride is directly injected into the gestational sac within the tubal lumen to induce resorption or absorption. In 1987 Feichtinger and Kemeter reported the first successful treatment of ectopic pregnancy by the injection of methotrexate.

Prostaglandins

Prostaglandins cause strong tubal muscular contractions and are local vasoconstrictors. Due to side effects like vomiting and abdominal cramps attempts using prostaglandin E2 injections directly into ectopic gestations were abandoned. Direct injections of prostaglandin f2 alpha into the affected tube and the ovary containing the corpus luteum was successful in 24 (92%) of 26 patients and Husslein et l reported and 84% success rate in 152 patients in eight centers in Austria. Lindblom and associates treated 9 women laparoscopically directed transtubal injections of prostaglandin f2 alpha. Complications like ventricular arrhythmias, transitory hypertension with pulmonary edema were experienced, which were attributed to concomitant injection of PG f2 alpha into the ovary.

Hyperosmolar Gulcose

Hyperosmolar glucose has been injected either laparoscopically or by transvaginal ultrasound guidance.

Potassium Chloride

Potassium chloride has been used for salpingocentesis. Robertson and associates injected a 20% potassium chloride solution into three tubal gestations. One case included a heterotopic pregnancy with co-existing intrauterine and cornual pregnancies. The authors were successful in resorption of cornual pregnancy without disturbing the intra uterine pregnancy. The other two patients did not have successful treatment and ultimately required laparotomy.

SURGICAL TREATMENT OF ECTOPIC PREGNANCY

Salpingotomy Versus Salpingectomy

In the presence of a healthy contra lateral tube there is no clear evidence that salpingotomy should be used in preference to salpingectomy.

Laparoscopy

In the haemodymaically stable patient, laparoscopic approach to the surgical management of ectopic pregnancy, is preferable to an open approach.

MATERIALS AND METHODS

All patients admitted to Institute of Obstetrics and Gynecology, with diagnosis of unruptured ectopic pregnancy managed medically between August 2011 and July 2012 were included in the study. The diagnosis of tubal pregnancy was made using both Transvaginal Sonography (TVS) and measurement of β-hCG level. Ectopic pregnancy was diagnosed when adnexal mass or extra uterine tubal gestational sac without intrauterine gestation was observed with TVS and when patients had inappropriately rising β-hCG levels. Patients who were hemodynamically unstable and who refused medical treatment with MTX and close follow-up were treated surgically.

The patients who were managed medically with methotrexate were categorized into 5 groups for follow up based on initial β-hCG levels. (<2500) mIU/ml, (2500-5000) m IU/ml,and (7500-10000) m IU/ml .

Patients with very low β-hCG levels (<200 m IU/ml) were managed expectantly.

Single dose methotrexate regimen was followed for patients with β-hCG levels ranging from 200m IU/ml to 6984 m IU/ml.

Multiple dose methotrexate regimen was followed for patients with β-hCG levels more than 7500 m IU/ml.

Before treatment with methotrexate, patients were counseled about the benefits and risk of treatment, the expected course and duration of treatment, and the importance of follow-up. Blood grouping and typing was done for all the patients and Anti-D immunoglobulin (2501U or 50 micrograms) administered to all Rh Negative mothers. All patients gave their informed consent before beginning the treatment.

Inclusion Criteria

- Patients who came with amenorrhea , abdominal pain, bleeding or spotting P/V and were diagnosed to have ectopic pregnancy after doing:
    1. Urine Pregnancy Test
    2. Trans vaginal sonography
    3. Serum β-hCG Levels
- Hemodynamically stable patients without active bleeding or signs of hemoperitoneum.
- Patients desiring future fertility
- Patients willing for follow up care
- No contraindication to MTX therapy

Exclusion Criteria

- Hemoperitoneum or hemodynamically unstable patients
- Contraindication to MTX therapy

    1. Breastfeeding
    2. Overt evidence of immunodeficiency
    3. Alcoholism /other chronic liver disease
    4. Pre existing blood dyscrasias
    5. Known sensitivity to methotrexate
    6. Active pulmonary disease
    7. Peptic ulcer disease
    8. Any chronic renal disorder

Single Dose Regimen

After doing Hemoglobin level, Total Count/Differential Count, Platelet Count, Renal function tests, Liver function tests and Serum β-hCG , on DAY 1,single intramuscular dose (1mg/kg) of methotrexate was given. On Day four and seven after the injection, β-hCG levels were measured. Patients received a repeat injection of MTX on Day 7 if their β-hCG levels failed to decline by atleast 15% between Day four and seven, and the protocol was restarted as Day 1.If the repeat β-hCG level

on Day 7 showed more than 15% fall when compared to Day 4, weekly follow up was done till levels <5mIU/ml. A successful response to MTX was defined as the resolution if the β-hCG level < 5mIU/mL. However, patients who required second dose of MTX due to inadequate fall in β-hCG levels by Day 7 were considered as failure of single dose regimen but successful medical treatment. With signs of tubal rupture, surgery was done.

All continuous variables are expressed as the mean ±SD. For statistical analysis, T-test and Chi-square test were used.

Multiple Dose Regimen

As in single dose regimen, these patients also underwent investigations, namely Hemoglobin levels, Total Count/Differential Count, Platelet count,Kidney function tests,LFT and serum β-hCG levels. Inj. Methotrexate (1 mg/kg) intramuscular was given on DAY 1, 3, 5 & 7 of the protocol followed by Inj. Leucovorin (0.1 mg/kg) on DAY 2,4,6 & 8.Serum β-hCG levels were repeated every alternate day from Day 3 onwards.

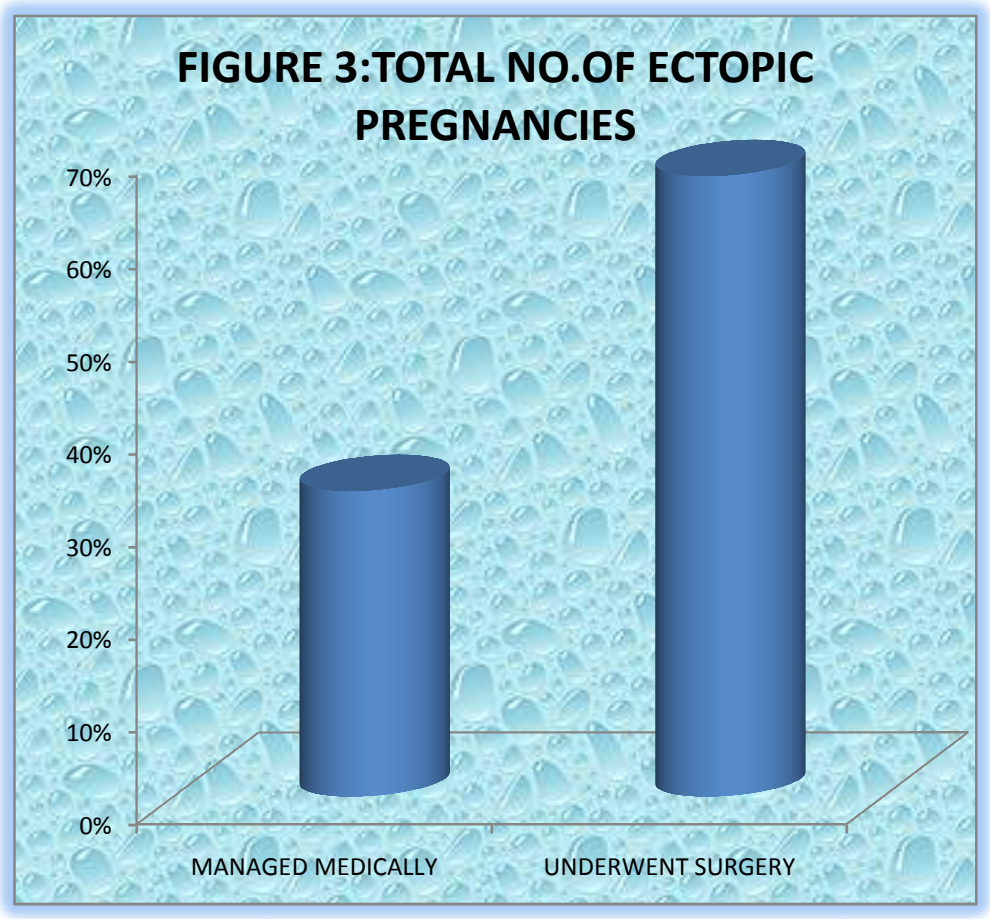
Complete blood and platelet count along with renal and liver function tests were repeated at the end of protocol to see any adverse effects of the drug. Weekly titres of β-hCG were done till they were <5 m IU/ml. However treatment was declined when a decline of >15% was observed in two consecutive counts of serum β-hCG after Day 3, or after completion of four dose of methotrexate (MTX). These patients were also followed up with weekly titers of β-hCG.

Expectant Management

With serial β-hCG measurements twice weekly was done to ensure a rapidly decreasing β-hCG level and transvaginal ultrasound examinations weekly to see the decrease in the size of adnexal mass by 7 days. Thereafter, weekly β-hCG and transvaginal ultrasound examinations were advised till serum β-hCG levels were < 5 mIU/ml.

OBSERVATIONS AND RESULTS

Total number of cases of ectopic tubal pregnancy from August 2011 to July 2012 were 119. Out of these 119 cases , 39 were managed medically during the same period (32.7%).

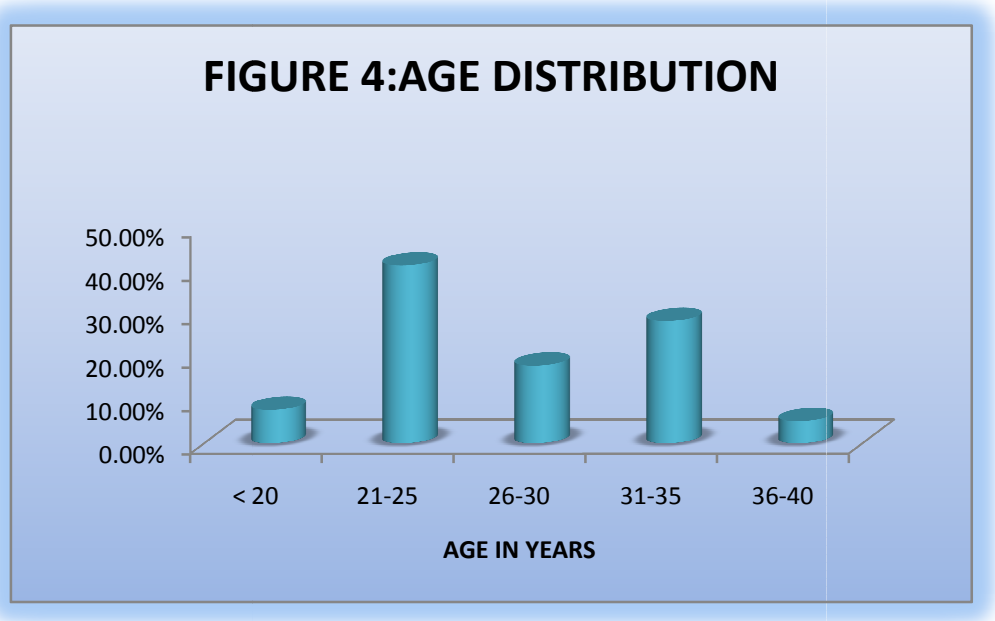


AGE DISTRIBUTION:

Age of patients in the study range from 19 to 36 years with mean age of 27.3 years ± 5.50 SD. The age distribution was as follows:

Table 9:Age Distribution(n=39)

AGE GROUP	n=39	%
< 20	3	7.7
21-25	16	41.0
26-30	7	17.9
31-35	11	28.2
36-40	2	5.1
Total	39	100.0

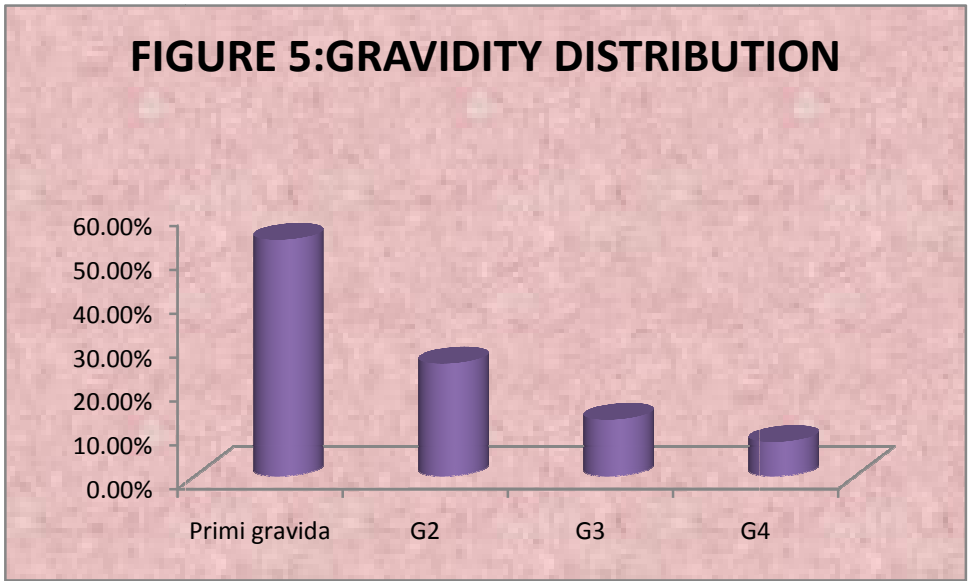


GRAVIDITY DISTRIBUTION:

Among the patients studied, 21% were primigravida and 10% were second gravidas. The gravidity distribution in the groups was as follows:

Table 10: Gravidity Distribution

GRAVIDITY	n=39	%
Primi gravida	21	53.8
G2	10	25.6
G3	5	12.8
G4	3	7.7
Total	39	100.0



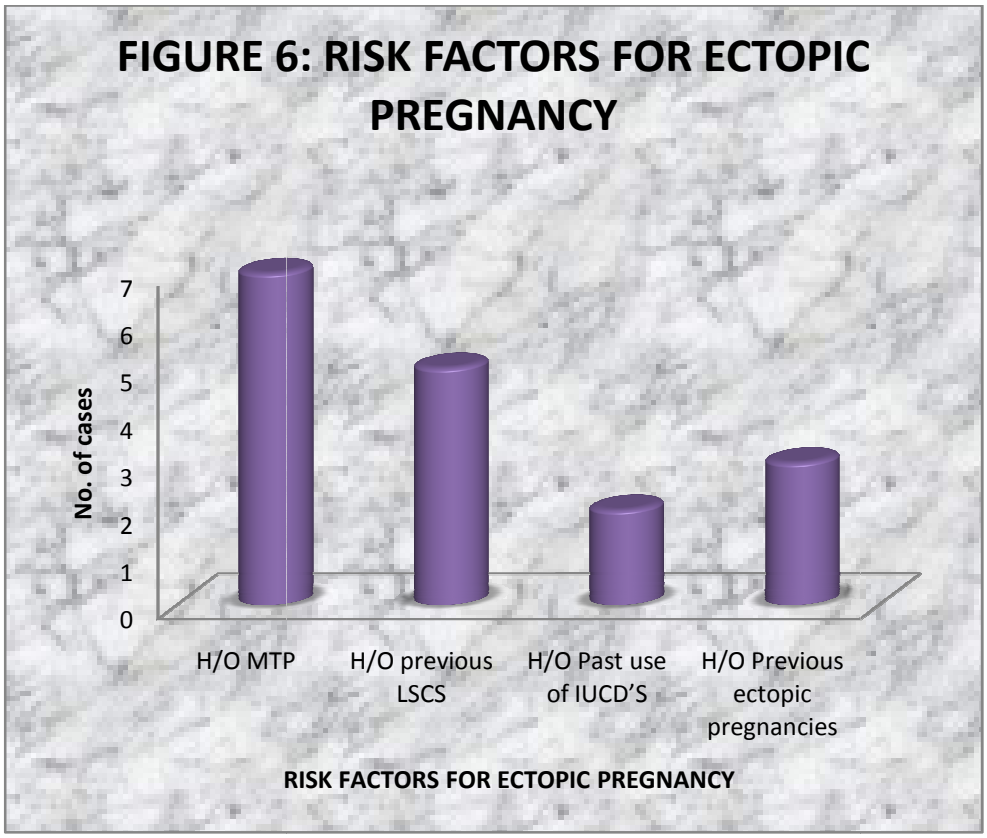
ASSOCIATED RISK FACTORS FOR ECTOPIC PREGNANCY:

Various associated factors which increase of risk of ectopic pregnancies were studied in the 39 cases. 17 out of total 39 had an associated risk factors and the commonest risk factor was found to be Medical termination of pregnancy(17.9%) followed by previous LSCS (12.8%).

The risk factors was as follows:

Table 11: Associated Risk Factors For Ectopic Pregnancy

RISK FACTOR	**n=17**	**%**
H/O MTP	7	17.9
H/O previous LSCS	5	12.8
H/O Past use of IUCD'S	2	5.1
H/O Previous ectopic pregnancies	3	7.7



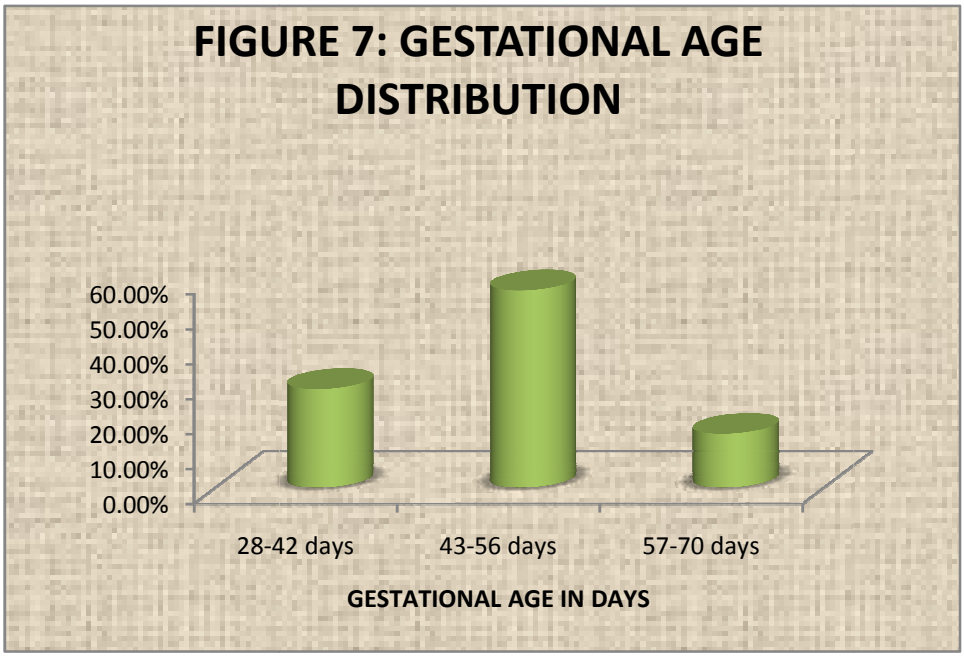
Medical termination of pregnancy
Lower segment caesarean section
Intra uterine Cu-devices

GESTATIONAL AGE DISTRIBUTION:

Among the patients studied gestational ranged from 28 to 70 days with mean gestational age of 48.2 days ± 9.03 SD. Maximum number of patients at gestational age between 43 to 56 days. i.e 56.4%. The gestational age distribution is as follows:

Table 12: Gestational Age:

GESTATIONAL AGE	n=39	%
28-42 days	11	28.2
43-56 days	22	56.4
57-70 days	6	15.4
Total	39	100.0



β-hCG LEVELS AT PRESENTATION:

In the study group, the distribution of β-hCG levels were studied. The maximum number of patients had their β-hCG levels between 200-2500 m IU/ml. The distribution of β-hCG levels was as follows:

Table 13: B-hCG Levels At Presentation

Initial β-hCG levels (m IU/ml)	**n=39**	**%**
< 200	5	13
201-2500	18	46.8
2501 -5000	4	10.4
5001-7500	7	17.9
7501-10000	5	13
Total	**39**	**100.0**

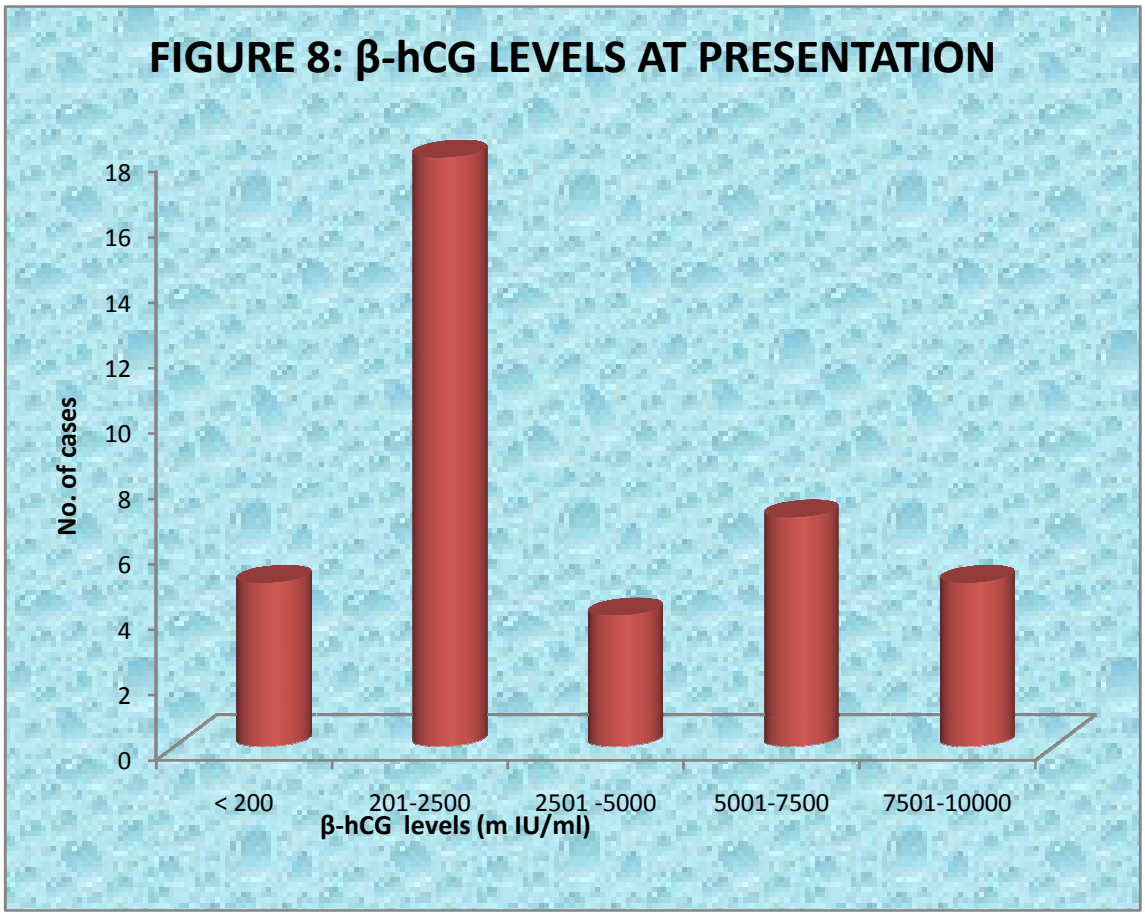


FIGURE 8: β-hCG LEVELS AT PRESENTATION
No. of cases
18
16
14
12
10
8
6
4
2
0
< 200
201-2500
2501 -5000
5001-7500
7501-10000
β-hCG levels (m IU/ml)

ADNEXAL MASS SIZE AT PRESENTATION:

Maximum number of patients i.e 56.4% had their adnexal mass size between 2-3 cms.The distribution of adnexal mass size at presentation was as follows:

Table 14: Adnexal Mass Size at Presentation

Adnexal Mass Size	n=39	Percent
0-1cm	3	7.7
1-2cm	13	33.3
2-3cm	22	56.4
> 3cm	1	2.6
Total	39	100.0

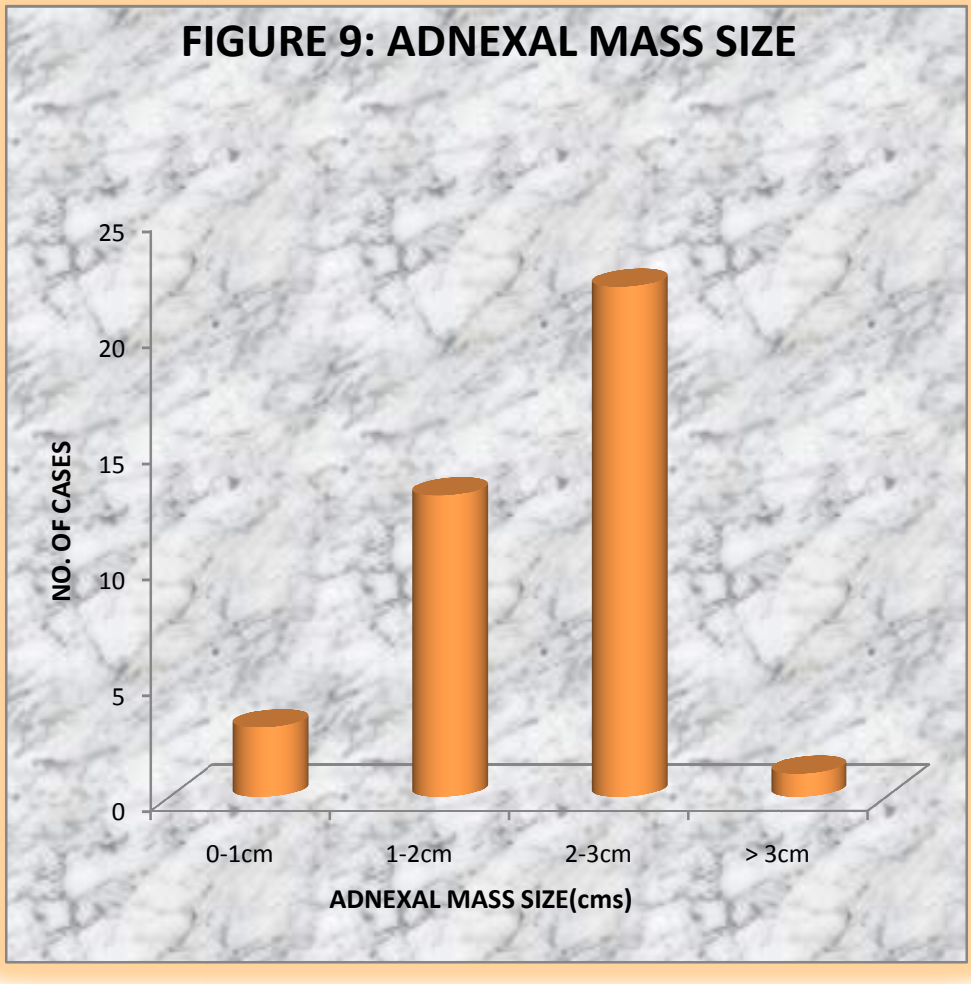


FIGURE 9: ADNEXAL MASS SIZE
NO. OF CASES
25
20
15
10
5
0
0-1cm
1-2cm
2-3cm
> 3cm
ADNEXAL MASS SIZE(cms)

METHOTREXATE REGIMEN DISTRIBUTION

Out of 39 patients 29 were managed with single dose of intramuscular methotrexate injection, 1 mg/kg, where as 5 patients were given multiple doses of methotrexate as they presented with β-hCG level more than 7500 mIU/ml. 5 patients were not given any dose of methotrexate as they presented with very low levels of β-hCG level i.e <200 m IU/ml. The distribution of various methotrexate regimen was as follows:

Table 15: Methotrexate Regimen Distribution

Medical treatment with methotrexate	n	Percent
Expected management	5	12.8
Single Dose Regimen	29	74.4
Multiple Dose Regimen	5	12.8
Total	**39**	**100.0**

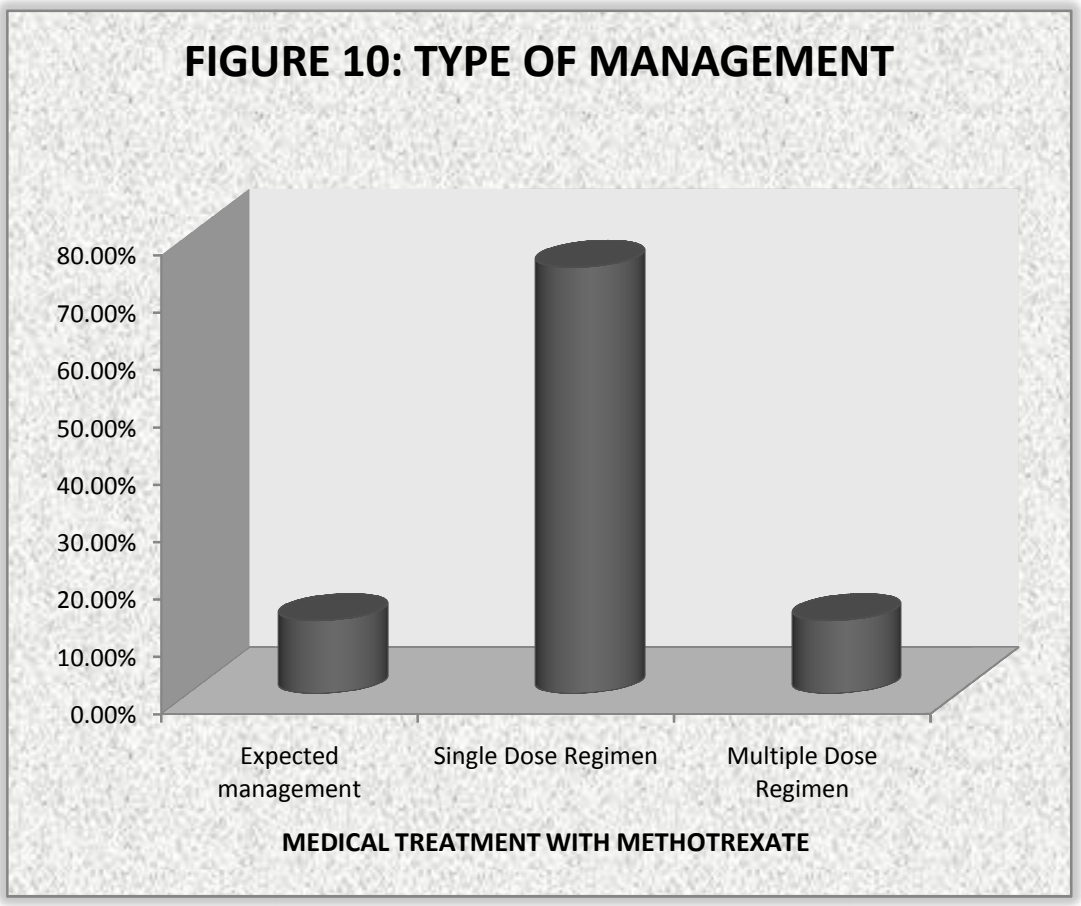


FIGURE 10: TYPE OF MANAGEMENT
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
Expected management
Single Dose Regimen
Multiple Dose Regimen
MEDICAL TREATMENT WITH METHOTREXATE

SINGLE DOSE REGIMEN-OUTCOME OF TREATMENT

Of the 29 patients treated with single dose regimen 22(76%) resolved with single dose, 3(10.3%) required repeat second dose, and 4(13.7%) were managed surgically before day 7 due to severe pain abdomen or evidence of hemoperitoneum. The outcome of treatment was as follows:

Table 16: Outcome Of Treatment-Single Dose Regimen

OUTCOME OF TREATMENT	n=29	%
Resolved with single dose	22	76
Required repeat second dose	3	10.3
Underwent surgery	4	13.7
Total	**29**	**100**

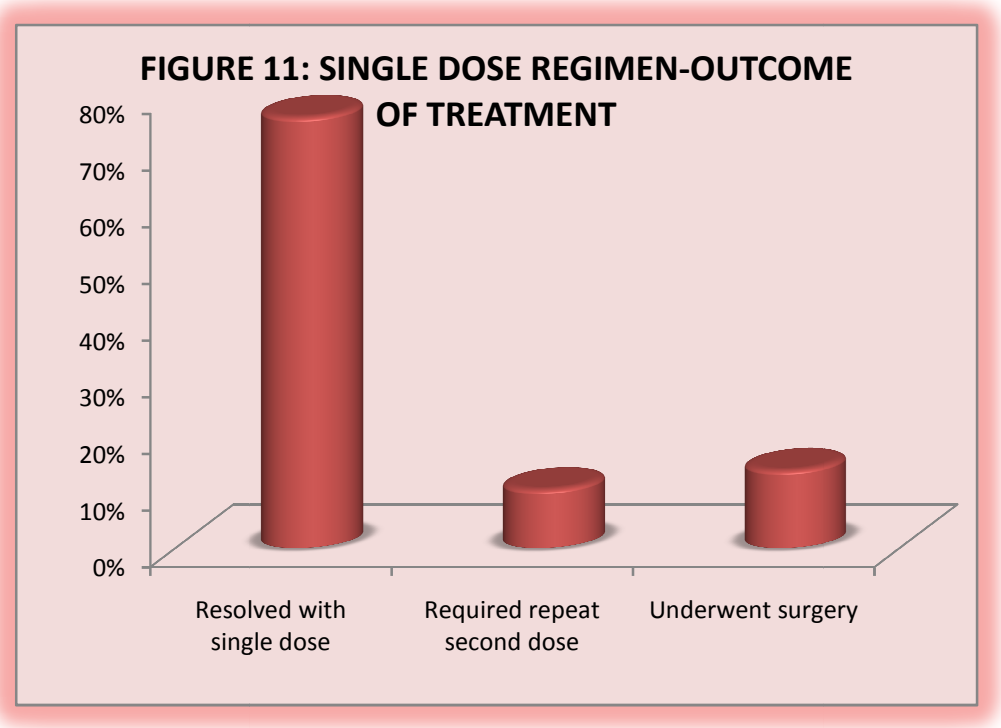


FIGURE 11: SINGLE DOSE REGIMEN-OUTCOME OF TREATMENT
80%
70%
60%
50%
40%
30%
20%
10%
0%
Resolved with single dose
Required repeat second dose
Underwent surgery

FINAL OUTCOME IN ASSOCIATION WITH INITIAL β-hCG LEVELS:

Among the patients given single dose methotrexate, 18 had β-hCG levels than 2500mIU/ml, 4 had levels between 2500-5000 m IU/ml and 3 patients had β-hCG levels from 5000-7500 mIU/ml. Among the 5 patients treated with multiple dose regimen, 5 patients presented with β-hCG levels between 7500-10000 mIU/ml. The association of outcome with initial β-hCG levels is as follows (p value<0.05 significant):

Table 17:Day1 hCG levels gps * OUTCOME * Methrotrexate regimen

Methotrexate regimen			OUTCOME				
			Resolved	%	Underwent surgery	%	Total
Expectant Management	Day1 hCG level gps	less than 200	5	100%	-	-	5
		Total	5				5
Single Dose Regimen	Day1 hCG level gps	201-2500	18	62%	0	-	18
		2501-5000	4	13.7%	0	-	4
		5001-7500	3	10.3%	4	13.7%	7
		Total	25		4		29
Multiple Dose regimen	Day1 hCG level gps	7501-10000	2	40%	3	60%	5
		Total	2		3		5

P value<0.05, hence statistically significant association was found between initial β-hCG levels and outcome of treatment with methotrexate in single dose regimen.

OUTCOME IN ASSCOCIATION WITH ADNEXAL MASS SIZE

Out of 29 patients who were treated with single dose regimen of methotrexate, 11 patients had adnexal size less than 2cms where as 18 had adnexal size more than 2cms. Out of 5 patients who were treated with multiple dose regimen, 1 patient had adnexal size less than 2cms, where as 4 had adnexal mass more than 2cms. The outcome in assocociation with adnexal mass size is as follows:

Table 18: Outcome In Asscociation With Adnexal Mass Size

Methotrexate regimen			OUTCOME				
			resolved	%	Underwent surgery	%	Total
Expectant Management	Mass Size	2cm and less	4	80%	-	-	4
		More than 2cm	1	20%	-	-	1
		Total	5	-	-	-	5
Single Dose Regimen	Mass Size	2cm and less	11	38%	0	-	11
		More than 2cm	14	48.2%	4	13.8%	18
		Total	25	-	4	-	29
Multiple Dose Regimen	Mass Size	2cm and less	1	20%	0		1
		More than 2cm	1	20%	3	60%	4
		Total	2	-	3	-	5

P value >0.05, hence no statistical significance was found between adnexal mass size and outcome of treatment in single dose regimen and multiple dose regimen.

OUTCOME IN ASSOCIATION WITH PERIOD OF AMENORRHEA

Out of 29 patients treated with single dose regimen, 9 patients had amenorrhea less than 42 days and 16 presented with amenorrhea more than 42 days. Out of 5 patients treated with multiple dose regimen, all patients presented with amenorrhea more than 42 days. The outcome of treatment in association with period of amenorrhea is as follows:

Table 19: Outcome in Association With Period of Amenorrhea

Methotrexate regimen	Gestational Age	OUTCOME				
		Resolved	%	Underwent surgery	%	Total
Expectant Management	<42 days	2	40%	-	-	2
	> 42 days	3	60%	-	-	3
	Total	5	-	-	-	5
Single Dose Regimen	<42 days	9	31%	-	-	9
	>42 days	16	55.2%	4	13.8%	20
	Total	25	-	4	-	29
Multiple Dose Regimen	> 42 days	2	40%	3	60%	5
	Total	2	-	3	-	5

P value >0.05, hence no statistical significance was found between period of amenorrhea and outcome of treatment.

DISSCUSSION

This prospective observational study includes all the patients who were diagnosed to have unruptured ectopic pregnancy by Transvaginal sonography(TVS) and serial beta β-hCG levels, and were managed medically with methotrexate.

39 patients with unruptured ectopic pregnancy were enrolled in the study and were observed for outcome of treatment with methotrexate.

The mean age of these 39 patients was 27.3 years ± 5.50 SD. Maximum patients belong to 20-29 years i.e.58.9%. The range was 19 to 36 years.

Mean gravidity of the patients studied was 1.74 ± 0.99 SD. Maximum patients were primigravidas or second gravidas .

Mean gestational age of all patients was 48.2 days ± 9.03 SD. Maximum number of patients had gestational age between 6-8 weeks.

Out of the 39 patients who were included in this study, 29 were managed with single dose regimen, 5 were managed with multiple dose regimen, 5 were managed expectantly.

Table 20: Unruptured Ectopic Pregnancies (n=39)

Medical treatment with methotrexate n=39		**Expectant management**
Single dose regimen	Multiple dose regimen	n=5
n=29	n=5	

Expectant management:

5 out of 39 patients, who were managed expectantly, were not given any dose of methotrexate as the patients did not have any symptoms or initial β-hCG levels were very low(<200 m IU/ml). They were followed up twice weekly with serial β-hCG measurements and weekly by transvaginal ultrasound examinations to ensure a rapidly decreasing β-hCG level (ideally <50% of its initial levels within 7 days) and a reduction in the size of adnexal mass by seven days. Thereafter, weekly β-hCG and transvaginal ultrasound examinations were advised until serum β-hCG levels were less than 5 m IU/ml.

In the present study, 5 patients were managed expectantly. The average initial β-hCG levels in these 5 patients were found to be 177.6 mIU/ml ± 27.7 SD. The average adnexal mass size at presentation was found to be 1.62 cms ± 0.38 SD. The average period of amenorrhea was found to be 47 days ± 7.87 SD. These patients were managed as per above mentioned protocol and complete resolution was seen in 5 patients,with an average time for complete resolution being 19.4 days ± 12.05 SD.

Methotrexate regimen for unruptured ectopic pregnancy

Single Dose Regimen:

Out of 39 patients, 29 patients were given single dose Inj. Methotrexate 1mg/kg.

1. **Age:** The mean age of these 29 patients was 27.27 yrs ± 5.11 SD. Maximum patients belonged to age group of 20 to 29 yrs and the range being 20 to 36 years.
2. **Gestational Age:** The mean gestational age of these 29 patients was found to be 46.3 days ± 8.45 SD. With range between 30 to 65 days.

3. **Gravidity :** The mean gravidity amongst these 29 patients was found to be 1.51.
4. **B-hCG levels at presentation:** The average initial β-hCG levels in the patients given with single dose of methotrexate was found to be 2683.02 m IU/ml. The range was found to be between 400 m IU/ml and 6600 m IU/ml.
5. **Outcome of Treatment:** 29 patients in this study were given single dose of 1mg/kg Inj. Methotrexate intramuscular. However, 25 responded to medical management with methotrexate without any surgical intervention. The end point of treatment i.e. complete resolution in these patients mean fall of β-hCG to <5mIU/ml without any surgical intervention.

Remaining 4(13.7%) went for laparotomy before day 7 because patients presented with severe abdominal pain or had evidence of hemoperitoneum.

Out of the 25 patients treated with methotrexate, 22(76%) resolved with single dose of methotrexate, hence successfully managed with single dose regimen and remaining 3(10.3%) required repeat second dose of

methotrexate on the 7th day due to inadequate fall in β-hCG level (<15%) by day 7, when compared to day 4 levels of β-hCG.

Single Dose Regimen: Outcome of Treatment

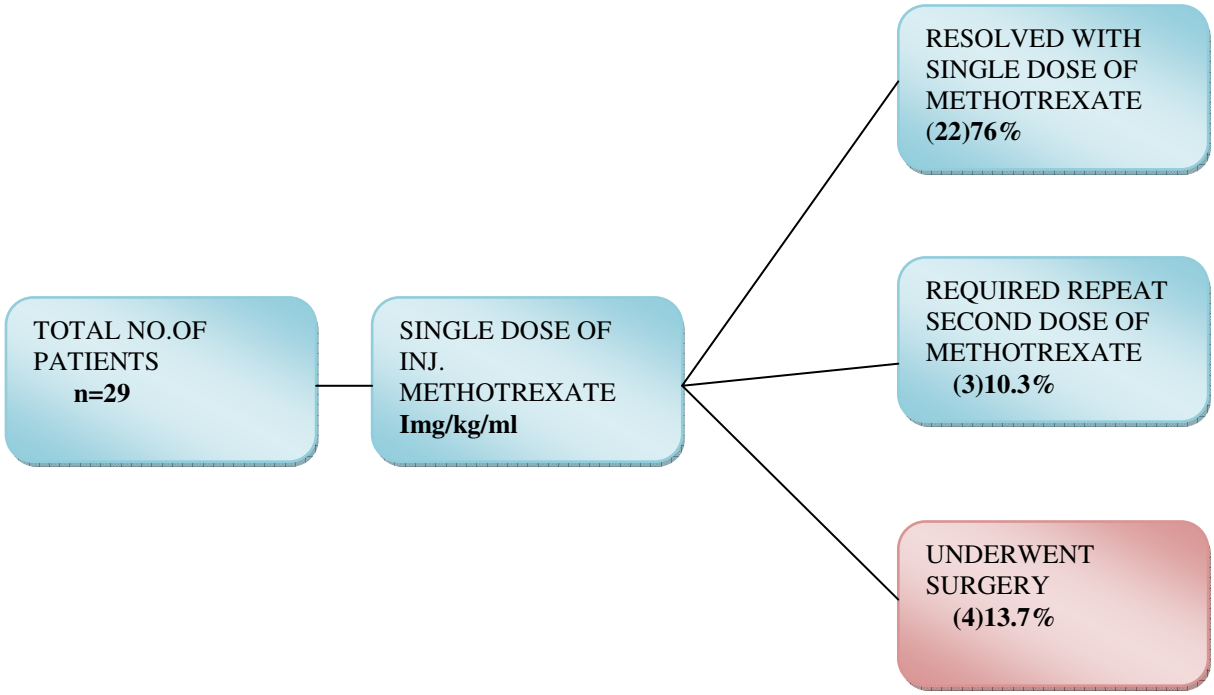


Figure: 12

The outcome of recent study was found comparable to the study done by Thia EWH et al in K.K Women's and Children Hospital , Singapore during a period of August 2003 to October 2006, who found 79.1% success rate of single dose of methotrexate (1mg/kg im) given to

110 patients presenting with unruptured ectopic pregnancy. 1 patient was lost for follow up during this period hence was excluded from the study.

A similar study done by Mamdoh et al showed a success rate of 94.3% in 70 patients diagnosed with unruptured ectopic pregnancy.

Table 21: Single Dose Regimen- Outcome of Treatment.

Study (n)	Resolved with Single dose n(%)	Required repeat second dose n(%)	Underwent surgery n(%)
Thia EWH et al(110)	87(79.1)	6(5.4)	16(14.5)
Merisio et al(11)	10(90)	1(10)	-
Mamdoh(70)	66(94.3)	3(4.3)	1(1.4)
Present study(29)	22(76)	3(10.3)	4(13.7)

6. Outcome of Treatment in Association with Initial β-hCG levels

Out of the 29 patients treated with single dose methotrexate regimen,18 had their initial β-hCG levels <2500 m IU/ml, 4 had their initial β-hCG levels between 2500-5000 m IU/ml and 7 had initial β-hCG

levels between 5000-7500 m IU/ml. Of these 22(75.7%) patients resolved with single dose of methotrexate. However,3(10.3%) patients required repeat second dose of methotrexate, 4(13.7%) patients went for laparotomy due to inadequate fall in β-hCG levels or persistence abdominal pain.

Statistically significant association was found between initial β-hCG levels and outcome of treatment. P value < 0.05 significant.

7. Outcome In Association With Adnexal Mass Size:

Patients presenting with adnexal mass size of less than 2cms i.e 11(38%) were successfully treated with single dose regimen and none went for laparotomy.Hence success rate of single dose regimen was found to be 38 % in those having adnexal mass size less than 2cms.

Patients presenting with adnexal mass of >2cms i.e.14 (48.2%) were successfully treated with single dose regimen, and 4(13.8%) went for laparotomy either due to severe abdominal pain or evidence of hemoperitoneum.

No statistical significant association was found between adnexal mass size and outcome of treatment (p value > 0.05).

8. Outcome in Association With Period Of Amenorrhea:

Of the 9(31%) patients presenting with period of amenorrhea less than 42 days, all resolved with single dose regimen -methotrexate therapy. None of the patients in this group went for laparotomy.

Of the 20(69%) patients presenting with amenorrhea more than 42 days, 16(55.2%)resolved with methotrexate therapy, 4(13.8) went for laparotomy.

No statistical significant association was found between period of amenorrhea and outcome of treatment. (p value > 0.05).

9. Outcome in Association with Cardiac Activity:

None of the patients in this study had presence of cardiac activity at time of presentation, hence could not be associated with the outcome.

10.Time Taken for Resolution: Average time taken for complete resolution of ectopic pregnancy in patients who resolved with single dose of methotrexate was found to be 20.44 days ± 7.6 SD.

Multiple Dose Regimen for Unruptured Ectopic pregnancies:

Out of 39 patients, 5 were treated with multiple doses of Inj. Methotrexate 1 mg/kg i.m.

1. **Age:** Mean age of these 5 patients was found to be 29.6 yrs ± 7.43 SD and the range being 21 to 36 yrs.
2. **Gravidity:** The mean gravidity of the patients in multiple dose regimen was found to be 2.6. The range was found to be between 1 and 4.
3. **Gestational Age:** The mean gestational age amongst these patients was found to be 57.4 days ± 9.68 SD. The range of gestational age was between 43 to 70 days.
4. **Initial β-hCG Levels at Presentation:** The mean initial β-hCG levels amongst these 5 patients was found to be 7688.4 m IU/ml ± 5379.9 SD. These patients treated with multiple dose regimen of methotrexate had β-hCG levels more than 7500 m IU/ml.

5. **Outcome of Treatment**

Out of the 5 patients treated with multiple dose regimen, 2(40%) resolved with methotrexate where as 3(60%) went for laparotomy due to persistent abdominal pain or evidence of hemoperitoneum.

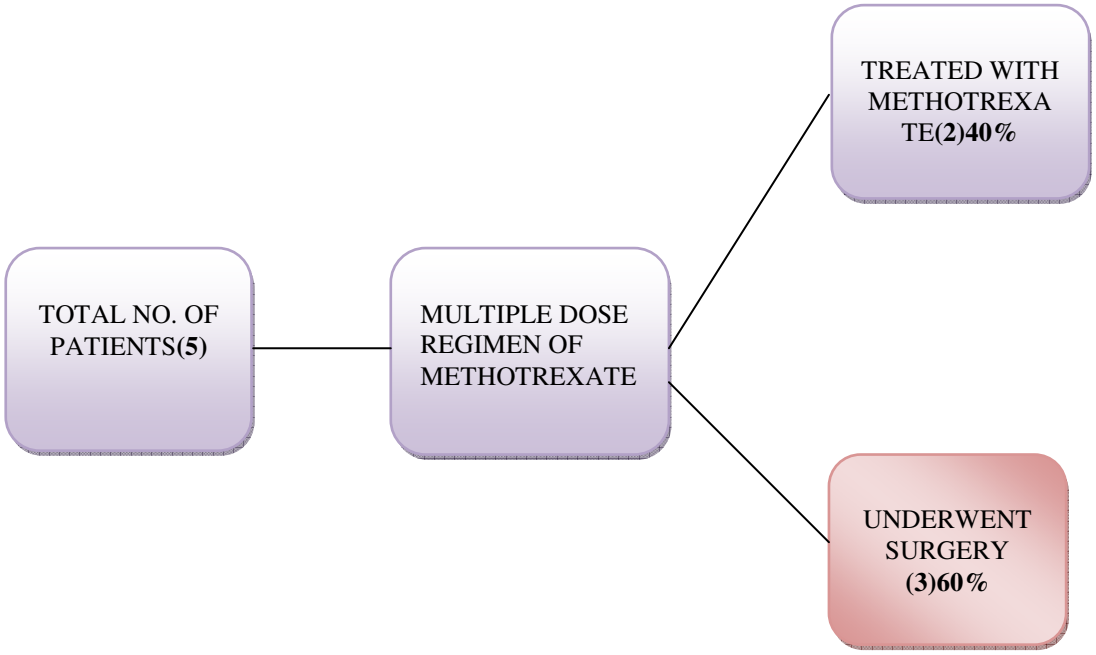


Figure: 13

6.Outcome of Treatment in Association with Initial β-hCG levels

The 5 patients who were treated with multiple dose regimen of methotrexate had β-hCG levels >7500 mIU/ml. Out of the 5 patients treated with multiple dose regimen, 2(40%) resolved with methotrexate where as 3(60%) went for laparotomy due to persistent abdominal pain or evidence of hemoperitoneum. The average initial β-hCG levels in these 3 patients were found to be 9566 m IU/ml.

7. **Outcome in Association With Adnexal Mass Size:**

Of the 5 patients in multiple dose regimen, 1(20%) presented with adnexal mass size <2cms and treated with multiple dose of methotrexate. 4(80%) patients presented with adnexal mass size >2cms of which 3(60%) went for laparotomy due to severe abdominal pain.

No statistical significant association was found between adnexal mass size and outcome of treatment (p value > 0.05).

8. Outcome in Association With Period Of Amenorrhea:

Of the 5 patients treated with multiple doses methotrexate, all patients with amenorrhea >42days, 2(40%) patients resolved with medical treatment where as 3(60%) required surgical intervention.

9. Outcome in association with cardiac activity

None of the patients in this study had presence of cardiac activity at time of presentation, hence could not be associated with the outcome.

10. Time Taken for Resolution: Mean time of resolution 2 patients out of 5 who resolved with multiple doses was 68.5 days ± 40.3 SD.

SUMMARY

- 39 cases of unruptured ectopic pregnancy which were managed medically with methotrexate were studied during the period of August 2011 to July 2012.
- Maximum incidence of unruptured ectopic pregnancy was found amongst the age group of 20 to 29 years.
- Commonest risk factor for ectopic pregnancy found in the study was Medical Termination of Pregnancy (17.9%), followed by previous LSCS being 12.8%.
- 13% of cases had β-hCG levels <200 m IU/ml, 46.8% of cases of unruptured ectopic pregnancies had their initial β-hCG levels between 200-2500 m IU/ml, 41.2 % of cases had β-hCG levels between 2500-10,000 m IU/ml.
- 56.4% of cases had adnexal mass size measuring between 2-3cms, 41% of cases presented with adnexal mass size <2cms, where as 59% of cases had initial adnexal mass size >2cms.
- Of the 39 patients studied, 28.2% patients had amenorrhea <42 days, 56.4% had amenorrhea between 43-56 days, and 15.4% had amenorrhea more than 57 days.

SINGLE DOSE REGIMEN

- In cases managed with single dose methotrexate regimen 75.7% resolved with methotrexate when the initial β-CG levels were <5000 m IU/ml. 13.7% underwent surgery when the initial β-CG level >5000 m IU/ml (p value<0.05) significant.
- None of the cases with adnexal mass size <2cms with single dose regimen went for laparotomy where as 13.8% of cases with mass size >2cms went for laparotomy. (p value>0.05)not significant.
- 13.8% of cases with amenorrhea >42 days in single dose methotrexate regimen went for laparotomy where as all those with amenorrhea <42 days resolved medically (p value>0.05) not significant.
- The association of outcome in relation to presence of cardiac activity could not be studied as none of the patients with presence of cardiac activity were treated with single dose methotrexate regimen.

MULTIPLE DOSE REGIMEN

- In cases managed with multiple dose methotrexate regimen 40% resolved with methotrexate when initial β-CG levels were between 7500-10000 m IU/ml and 60% underwent surgery.
- None of the cases with adnexal mass <2cms in multiple dose regimen went in for laparotomy where as almost 60% of patients with adnexal mass >2cms went in for laparotomy(p value>0.05) not significant.
- In cases managed with multiple dose regimen, 40% resolved with methotrexate when period of amenorrhea >42days and 60% underwent laparotomy when period of amenorrhea was >42days.
- The association of outcome in relation to presence of cardiac activity could not be studied as none of the patients with presence of cardiac activity were treated with multiple dose methotrexate regimen.

EXPECTANT MANAGEMENT

- All patients in expectant management group resolved spontaneously, and average initial β-hCG level <200 m IU/ml and time of resolution being 19.4 days.

CONCLUSION

- Complete resolution was seen in all cases of single dose methotrexate regimen whose mean initial β-hCG was 2683 m IU/ml, adnexal mass<2cms and amenorrhea <42days.
- Statistically significant association was seen between the initial β-hCG levels and with outcome of treatment. No statistical significance was found between adnexal mass size at presentation, period of amenorrhea and outcome of treatment in single dose regimen.
- In cases managed with multiple dose methotrexate regimen, complete resolution was seen in those having mean initial β-hCG of 7688.4 mIU/ml and adnexal mass size <2cms.
- No statistically significant association was found between adnexal mass and outcome of treatment in multiple dose regimen.

- However no association could be assessed between cardiac activity and outcome of treatment as none of the patients with cardiac activity were treated with methotrexate regimen.
- However, more studies including more number of patients need to be done to assess the correlation between outcome of medical management of unruptured ectopic pregnancy with methotrexate and initial β-hCG levels, adnexal mass size, and period of amenorrhea and presence of cardiac activity.

BIBLOGRAPHY

1. **Hage PS, Arnoulk IF, Zarou DM et al.** Laproscopic management of ovarian pregnancy, *J Am Assoc Gynecol Laprosc 1994;283-285,*
2. **Bouyer J, Coste J Ferrnandez H et al.** Sites of ectopic pregnancy; a 10 year population based study of 1800 cases. *Hum Reprod 2002:17:3224-3230.*
3. **Ercal T, Cinar O, Mumcu A,Lacin S, Ozer E.** Ovarian pregnancy; relationship to an intrauterine device. *Aust N Z J Obstet Gynaecol 1997* Aug;37(3):362-4.
4. **Speert H,Otto** Spiegelberg and His criteria of Ovarian Pregnancy, *Obstetric and Gynecologic Milestones,* The MacMillan Company, New York, 1958:p.255f.
5. **Habbu J, Read.** Ovarian pregnancy successfully treated with methotrexate. *J Obstet Gynaecol 2006* Aug:26(6):587-8.
6. **Parente JT, Ou CS, Levy J, Legatt E.** Cervvical pregnancy analysis: a review and report of 5 cases. *Obstet Gynecol* 1983 July;62(1):79-82.

7. **Laughlin CL, Lee TG, Richards RC.** Ultrasonographic diagnosis of cervical ectopic pregnancy. *J Ultrasound Med* 1983; 2:137-8.
8. **Michael P. Diamond, Alan H. Decherney.** *Obstetrics and gynaecology clinics of North America;* March 1991: Vol 18 (19-35).
9. **Kadar N, Bohrer M, Kemmamm E, Shelden R.** The discriminatory human chorionic gonadotropin zone for endovaginal sonography: a prospective, randomized study. *Fertil Steril* Jun 1994;61(6):1016-20
10. **NOVAK'S TEXTBOOK OF GYNAECOLOGY**
11. **Erdal Malatyalioglu, Sinan Ozar, Arif Kokcu, Mehmet B.** Cetinkaya, Tayfun Alper, Migraci Tosun. *Journal of Obstetrics and Gynaecology*. 32:422-427.
12. **Sjoberg J.** Pregnancy-associated plasma protein-A in pregnancy-related gynecologic emergency. *Hum Reprod* 1987;2:615-6.
13. **Mol BW, Lijmer JG, Ankum WM, van der Veen F, Bossuyt PM.** The accuracy of single serum progesterone measurement in

the diagnosis of ectopic pregnancy: a meta-analysis. *Hum Reprod* 1998; 13:3220-7.

14. **Dart R, Ramanujam P, Dart L.** Progesterone as a predictor of ectopic pregnanacy when the ultrasound is indeterminate. *Am J Emerg Med* 2002; 20:575-9.

15. **GrossKinsky CM, Hage ML, Tyrey L, Christakos AC, Hughes CL.** B-hCG, progesterone, α-fetoprotein, and estradiol in the identification of ectopic pregnancy. *Obstetrics and Gynaecology* 1993; 81: 705-709.

16. **Kuscu E, Vicdan K, Turhan NO, Oguz S, Zorlu G, Gkmen O.** The hormonal profile in ectopic pregnancies. *Materia Medica Polnana* 1993; 25: 149-152.

17. **Felemban A, Sammour A, Tulandi T.** Serum vascular endothelial growth factor as a possible marker for early ectopic pregnancy. *Hum Reprod* 2002; 17:490-2227.

18. **Chandra L, Jain A.** Maternal serum creatine kinase as a biochemical marker of tubal pregnancy. *Int J Gynaecol Obstet* 1995; 49: 21-3.

19. **Farquhar CM.** Ectopic pregnancy.*Lancet.* 2005; 366:583-91.

20. **Williams text books of Gynaecology, 2nd Edition.**

21. **Willams text books of Obstetrics.**

22. **Segal S, Gor H, Correa N, Mercado R, Veenstra K, Rivnay B.** Inhibib A:marker for diagnosis of ectopic and early abnormal pregnancies. *Reproductive Biomedicine online* 2008; 17:789-794.

23. **Emma K, Bourne T,** Diagnosis of ectopic pregnancy with ultrasound; *Best practice and Research clinical Obstetrics and Gynaecology* 2009; 23:501-508.

24. **Barnhart K, Mennuti MT, Benjamin I.** Prompt diagnosis of ectopic pregnancy in an emergency department setting. *Obstet Gynaecol.* Dec 1994; 84(6):1010-5.

25. **Aleem FA, De Fezia M, Gintautas J,** Endovaginal sonography for early diagnosis of intrauterine and ectopic pregnanacy. *Human Reprod* 1990; 5(6):755-758.

26. **Murray H, Baakdah H, Bardell T, Tulandi T.** Diagnosis and treatment of ectopic pregnancy. *CMAJ,* 2005; 173:905-912.

27. **Shalev E, Yarom I, Bustan M, Weiner E, Ben Shlomo I.** Transvaginal sonography as the ultimate diagnostic tool for the management of ectopic pregnancy. 1998; 69: 62-65.

28. **Conodous G.** Ectopic pregnancy – risk factors and diagnoasis. *Aust Fam Physician.* 2006; 35:854-857.

29. **Kadar N, De Vore G, Romero R.** Discriminatory hCG zone use in the sonographic evaluation for ectopic pregnancy. *Obstet Gynaecol* 1981; 58:156-61.

30. **Shalev E, Peleg D Tsabari A, Romano S, Bustan M.** Spontaneous resolution of ectopic tubal pregnancy: natural history. *Fertil Steril.* 1995; 63:15-9.

31. **Moeller LB, MoellerC, Thomsen SG, Andersen LF, Lundvall L.** Success and spontaneous pregnancy rates following systemic methotrexate versus laproscopic surgery for tubal pregnancies.*Obstet Gynaecol Scand.* Sep 11 2009:1-7.

32. **Lipscomb GH, McCord ML, Stovall TG, Huff G, Portera SG, Ling FW.** Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. *N Engl J Med* 1999; 341:1976.

33. **Thia E W H, Loi K, Wang J J,Siow A.** Methotrexate treatment for ectopic pregnancy at the KK women's and children's hospital, Singapore. *Singapore Med J 2009; 50(11):1058.*

34. **Barnhart KT, Sammel MD, Hummel A, Jain J, Chaktoura N, Strauss J.**A novel "two dose" regimen of methotrexate to treat ectopic pregnancy.*Fertil Stertil.* 2005; 84(Suppl):S130.

35. **Carla Merisio, Salvatore Anfuso, Roberto Berretta, Mattia Gualdi, Dora Caterina Pultrone, Mauro Melpignano.** Single-dose methotrexate for ectopic pregnancy preliminary data. *ACTA BIO MED* 2005; 76;33-36.

36. **Mamdoh Eskandar.** Single dose methotrexate for treatment of ectopic pregnancy:risk factors for treatment failure.*Middle East Fertility Society Journal* 2007;12: No.1.

37. **Thurman R, Cornelius M, Korte JE,Fylstra DL.** An alternative monitoring protocol for single-dose methotrexate therapy in ectopic pregnancy. *Am J Obstet Gynecol.* Feb 2010; 202(2):139.

38. **Timor-Trisch I, Baxi L, Piesuer D.** Transvaginal saipingocentesis: A new technique for treating ectopic pregnancy . *Am J Obstet Gynecol 1989; 160:459.*

39. **RCOG GREEN TOP GUIDLINE NO.21; MAY 2004**

40.. ***Weekstein LN,*** Current prospective on ectopic pregnancy. *Obstet Gynaecol Surv.* 1985; 40:262.

41. **Pisarska MD, Carson SA, Burster JE.** Ectopic pregnancy .*Lancet 1998; 351: 1115-1120.*

42. **Shalev E, Peleg D, Bustan M, Romano S, Tsabari A.** Limited role for intratubal methotrexate treatment of ectopic pregnancy.*Fertil Sterrlil* 1995; 63;20-

PROFORMA

- NAME: AGE: IPNO: ADDRESS:
- OCCUPATION: DATE OF ADMISSION:
- DATE OF DISCHARGE:
- LMP: GESTATIONAL AGE:
- ADMISSION: OPD CASUALTY REFERRED

H/O PRESENTING ILLNESS:

- PERIOD OF AMENORRHOEA
- PAIN ABDOMEN
- URINARY COMPLAINTS
- BLEEDING/SPOTTING PV
- DISCHARGE PV
- NAUSEA/ VOMITING
- DIARRHOEA
- FEVER
- CONSTIPATION/ TENESMUS

MENSTRUAL HISTORY

No. of days

Length of cycle

RMC/IRMC

Martial History

Married for how long, Consanguinity

Contraception-OCPs/POPs/IUCD/Barrier/Tubal Sterilization

Obstetric History:

Gravida,Para,Live,Abortions

H/O Previous Ectopic

H/O Tubal Sterlization

H/O Assisted Reproductive Technique's

H/O Previous LSCS

H/O Hysterosalpingography

Past Medical History: DM/HT/BA/TB/Thyroid Disorders/Epilepsy/Heart Disease

Past Surgical History:

Tubal recanalization / hysteroscopy

Laparoscopy/ D&C

Abortions

Any other surgeries

Family History:

On/Examination:

General condition

Vitals-

Blood Pressure

Pulse rate

Resp. Rate

Temp.

CVS/RS-

Per Abdomen-

- Tenderness
- Bowel Sounds
- Scars/sinuses
- Previous Scars
- Hernial Orifices

Per Speculum-

Per Vaginum-

- Size of Uterus
- Forniceal/cervical motion tenderness

INVESTIGATIONS

- HEMOGLOBIN, PCV, PT/APTT/INR
- PLATELETS , TOTAL COUNT , DIFFERENTIAL COUNT, LFT, RFT
- BLOOD GROUPING AND TYPING
- HBsAg, HIV, VDRL
- β-HCG LEVELS
- URINE PREGNANCY TEST
- TRANSVAGINAL SONOGRAPHY FINDINGS

- SAC SIZE
- CARDIAC ACTIVITY
- FLIUD IN POD
- FETAL POLE

Table 22: Mode of Treatment-single and Multiple Dose Regimen

Mode of treatment	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Single Dose MTX	✓						
β-HCG levels(single dose regimen)	✓			✓			✓
Multiple Dose MTX	✓		✓		✓		✓
Folinic Acid (0.1mg/kg)		✓		✓		✓	
β-HCG levels(multiple dose regimen)	✓		✓		✓		✓

Table 23: Outcome of Treatment in Different Regimens

Mode of Treatment	**Outcome**		
Expectant Management	Spontaneous Resolution	Underwent Surgery	
Single Dose Regimen	Resolved with Single Dose	Required repeat Second Dose	Underwent Surgery
Multiple Dose Regimen	Resolved with Methotrexate	Underwent Surgery	

PATIENT CONSENT FORM

STUDY TITLE: **A PROSPECTIVE STUDY ON THE OUTCOME OF MEDICALLY (METHOTREXATE) MANAGED CASES OF UNRUPTURED ECTOPIC TUBAL PREGNANCIES AT I.O.G.**

STUDY CENTRE: Institute of Obstetrics and Gynaecology, Egmore, Chennai.

PARTCIPANT NAME: AGE: I.D.NO:

I confirm that I have understood the purpose of the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my complete statisfaction.

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected.

I understand that investigator, the institution, regulatory authorities and the ethics committee will not need my permission to look at my health records both in respect to the current study and futher research that may be conducted in relation to it, even if I withdraw from the study. I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from the study.

I hereby consent to, undergo complete physical examination, and diagnostic tests including haematological , and ultrasonogram examinations for me.

I hereby consent to participate in this study on "TO STUDY ON THE OUTCOME OF MEDICALLY (METHOTREXATE) MANAGED CASES OF UNRUPTURED ECTOPIC TUBAL PREGNANCIES AT INSTITUTE OF OBSTETRICS AND GYNAECOLOGY".

Place: Signature of the Patient:

Date: Address:

Signature of the witness: Signature of Investigator:

S.NO	NAME	AGE	GRAVIDA	PARA	LIVE	ABORTION	ECTOPIC	GESTATIONAL AGE	MASS SIZE	CA	MTX DOSES	DAY 1 HCG	DAY 3 HCG	DAY 4 HCG	DAY 5 HCG	DAY 7 HCG	RESOLUTION	OUTCOME
1	Vijayalakshmi	25	2	1	1	0	0	38	1.4	Neg	0	187		74		67	35	Nil
2	Revathi	22	1	0	0	0	0	48	2.1	Neg	0	130		107		35	28	Nil
3	Chitra	19	1	0	0	0	0	50	1.25	Neg	0	178		106		97	18	Nil
4	Maheswari	21	1	0	0	0	0	56	1	Neg	4	8756	3520		3125	890	97	nil
5	Anupreethi	32	1	0	0	0	0	48	2.1	Neg	1	1600		1710		750	28	Nil
6	Arthibanu	22	1	0	0	0	0	43	1.9	Neg	2	5915		5680		5000	50	2nd dose
7	Lakshmi	28	2	0	0	1	0	56	2.5	Neg	1	476		350		248	10	Nil
8	Anusha	20	1	0	0	0	0	43	1.9	Neg	2	710		2330		2070	30	2nd dose
9	Prema	34	1	0	0	0	0	30	2.2	Neg	1	1770		230		200	12	Nil
10	Praveena	35	4	3	1	0	0	60	3.5	Neg	4	9,780	10,000					Lap
11	Madhani	29	3	1	1	1	0	58	1.98	Neg	0	197		154		60	7	Nil
12	Suseela	24	1	0	0	0	0	50	2.5	Neg	1	5390		5400		6000		Lap
13	Uma	29	1	0	0	0	0	52	2.9	Neg	1	2070		2080		325	10	Nil
14	Sundari	22	1	0	0	0	0	51	1.65	Neg	1	1370		1800		670	12	Nil
15	Panjala	34	3	1	1	1	0	58	3	Neg	4	9,890						Lap
16	llamathy	20	1	0	0	0	0	43	2.65	Neg	1	2530		3500		1100	22	Nil
17	Vaidagi	22	1	0	0	0	0	43	2.5	Neg	4	9,896	1,130			302.1	40	Neg
18	Sumithra	25	1	0	0	0	0	51	1.65	Neg	1	1267		1860		670	10	Nil
19	Kannagi	28	4	2	1	1	0	41	1.4	Neg	0	196	76				9	Neg

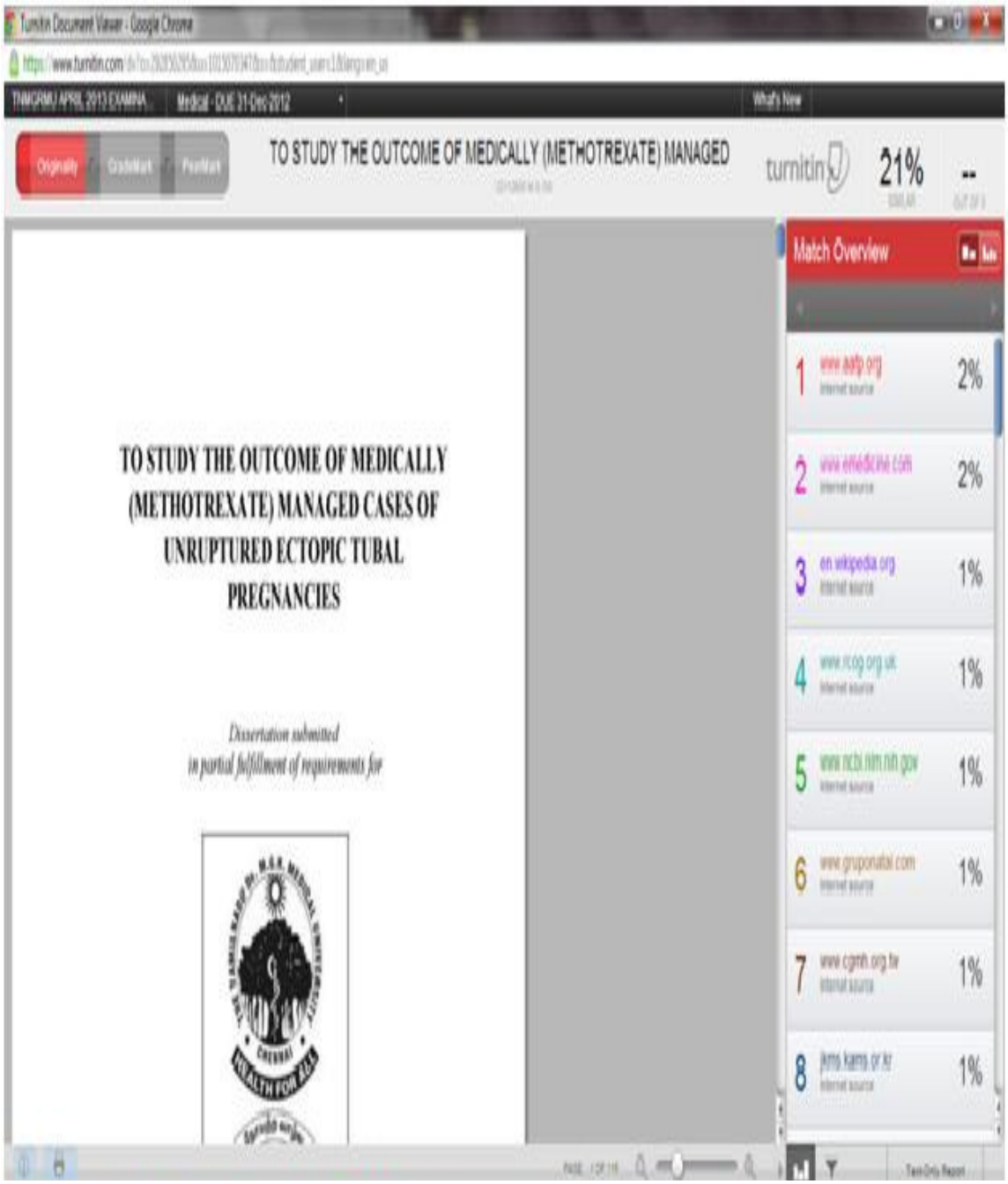
20	Parameswari	22	3	1	1	0	1	38	2	Neg	1	872.7		560		42.87	17	Neg
21	Sumathi	25	1	0	0	0	0	44	2.4	Neg	1	6984						Lap
22	Vani	30	2	1	1	0	0	36	1.5	Neg	1	2618		150		170	23	Nil
23	Megala	32	3	1	1	1	0	55	2.25	Neg	1	1680		2182		750	28	Nil
24	Vasanthi	22	1	0	0	0	0	35	1	Neg	1	400		976		200	16	Nil
25	Ragapriya	34	1	0	0	0	0	30	2.3	Neg	1	2010		220		170	23	Nil
26	Rani	21	1	0	0	0	0	45	2.25	Neg	1	1050		300		200	16	Nil
27	Selvi	35	2	1	1	0	1	65	2.9	Neg	1	6600		5190		6000		Lap
28	Vijaya	27	2	1	1	0	0	60	2.35	Neg	1	4185		4300		3275	30	Nil
29	Premila	36	2	0	0	1	0	48	2.6	Neg	1	980		900		350	26	Nil
30	Anandhi	33	3	1	1	1	0	41	0.9	Neg	1	1925		3135		2182	30	Nil
31	Karpagam	36	4	2	1	0	1	70	2.9	Neg	4	9030	9271					Lap
32	Suganthi	24	1	0	0	0	0	41	2	Neg	1	5390		5400		1080	20	Nil
33	Kasthuri	31	2	1	1	0	0	41	1.5	Neg	1	2005		1685		882	18	Nil
34	Malliga	23	1	0	0	0	0	53	1.65	Neg	1	500		400		196	23	Nil
35	Maheswari	32	2	1	1	0	0	40	2	Neg	1	5705		5900		1427	26	Nil
36	Roja	30	2	1	1	0	0	51	2.5	Neg	2	580		1600		1615	28	2nd dose
37	Arputham	25	1	0	0	0	0	55	2.3	Neg	1	2700		2000		1482	20	Nil
38	Ragavi	32	2	1	1	0	0	46	2.5	Neg	1	6625		7900		6001		Lap
39	Sheela	21	1	0	0	0	0	54	1.7	Neg	1	1900		2000		570	26	Nil

KEY TO MASTER CHART

CA	-	Cardiac activity
MTX	-	Methotrexate
β –Hcg	-	Beta subunit of human chorionic gonadotropin

ABBREVIATION

ART	-	Assisted reproductive techniques
CI	-	Confidence interval
Cms	-	Centimeters
DES	-	Diethylstilbesterol
EP	-	Ectopic Pregnancy
ET	-	Embryo transfer
GA	-	Gestational age
i.m	-	Intramuscular
IUCD	-	Intrauterine contraceptive device
IUP	-	Intrauterine pregnancy
IVF	-	In vitro fertilization
LSCS	-	Lower segment caesarean section
m IU/ml	-	Mili International units per Mililiter
mg/ kg	-	milligrams per kilograms
MTP	-	Medical termination of pregnancy
MTX	-	Methotrexate
PGE_{2a}	-	Prostaglandin E2 Alpha
PID	-	Pelvic inflammatory disease
POD	-	Pouch of Douglas
POP	-	Progesterone only pills
RCT	-	Randomised controlled trial
Rh	-	Rhesus factor
RR	-	Relative risk factor
TVS	-	Transvaginal ultrasonography
USG	-	Ultrasonography
β –hCG	-	Beta subunit of human chorionic gonadotropin


Turnitin Document Viewer - Google Chrome
TNMGRMU APRIL 2013 EXAMINA...
Medical - DUE 31-Dec-2012
What's New
Originality
GradeMark
PeerMark
TO STUDY THE OUTCOME OF MEDICALLY (METHOTREXATE) MANAGED
turnitin
21%
--
TO STUDY THE OUTCOME OF MEDICALLY (METHOTREXATE) MANAGED CASES OF UNRUPTURED ECTOPIC TUBAL PREGNANCIES
Dissertation submitted
in partial fulfillment of requirements for
Match Overview
1 www.adfp.org 2%
2 www.emedicine.com 2%
3 en.wikipedia.org 1%
4 www.rcog.org.uk 1%
5 www.ncbi.nlm.nih.gov 1%
6 www.gruponatal.com 1%
7 www.cgmh.org.tw 1%
8 jkms.kams.or.kr 1%